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EXPERIMENTAL RHEUMATOID MYOCARDITIS *

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The lesion found in the myocardium in acute rheumatic fever is considered the most characteristic anatomic feature of the disease, both by those who believe the streptococcus to be the exciting agent and by those who believe that the disease is produced by an unknown virus.

This characteristic lesion, first described by Aschoff [1] and by Geipel,[2] is an interstitial submiliary body composed, for the most part, of large mononuclear or multinucleated cells with vesicular nuclei. These cells show a characteristic staining reaction with methyl-green pyronin. Some lymphocytes and plasma cells and an occasional polymorphonuclear leukocyte are frequently present in these nodules. The nodules are generally located in the loose connective tissue of the myocardium, and commonly they are found in the tissues adjacent to medium sized blood vessels. A more or less diffuse interstitial and periarterial proliferative inflammation is generally associated with these submiliary bodies.

Nodular inflammatory areas have been produced experimentally in the myocardium of rabbits by intravenous injections of streptococci by Bracht and Wächter;[3] Jackson;[4] Coombs, Miller and Kettle;[5] Thalhimer and Rothschild,[6] and Rosenow.[7] Thalhimer and Rothschild think

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1. Aschoff, L.: Zur Myocarditisfrage, Verhandl. d. deutsch. path. Gesellsch. **8**:46, 1904; A Discussion on Some Aspects of Heart-Block, Brit. M. J. **2**:1103, 1906.

2. Geipel, P.: Untersuchungen über rheumatische Myokarditis, Deutsches Arch. f. klin. Med. **85**:75, 1906.

3. Bracht, E., and Wächter, O.: Beitrag zur Ätiologie und pathologischen Anatomie der Myocarditis rheumatica, Deutsches Arch. f. klin. Med. **96**:493, 1909.

4. Jackson, L.: Experimental "Reumatic Myocarditis," J. Infect. Dis. **11**:243, 1912.

5. Coombs, C.; Miller, R., and Kettle, E. H.: The Histology of Experimental Rheumatism, Lancet **2**:1209, 1912.

6. Thalhimer, W., and Rothschild, M. A.: Experimental Focalized Myocardial Lesions Produced with Streptococcus Mitis, J. Exper. Med. **19**:429, 1914.

7. Rosenow, E. C.: The Etiology of Acute Rheumatism, Articular and Muscular, J. Infect. Dis. **14**:61, 1914.

that all these experimental lesions lack the specific characteristics (location, structure and staining properties) of the human Aschoff nodule. Coombs, Miller and Kettle admit that there is a slight difference between the human and experimental nodular areas; but they think that this difference can be accounted for on the basis of the probable larger inoculations in the experimental cases. The illustrations of the nodules produced by Jackson compare favorably with the nodular lesions found in the human myocardium in cases of acute rheumatic fever.

To produce these Aschoff bodies experimentally in animals with a definite virus would, with the general present conception of the specificity of the Aschoff body, help toward establishing the etiologic relation of the virus to acute rheumatic fever. The purpose of the present work was to produce experimental myocarditis in rabbits and to compare it with human rheumatic myocarditis.

The bacterial observations from several cases of acute rheumatic fever were recently reported.[8] Streptococci, usually viridans strains, were commonly found. In cultivating blood taken from patients having acute rheumatic fever, the organisms when first seen in the liquid medium were regularly observed to be in clumps as if agglutinated. The blood from patients with rheumatic fever was found to contain agglutinins for certain strains of streptococci in dilutions of 1 : 50 and higher. It was suggested that the Aschoff nodule might develop as a result of clumps of agglutinated streptococci lodging in the small vessels in the heart. To simulate this condition as nearly as possible, a strain previously isolated from a case of acute rheumatic fever was agglutinated with its homologous serum. To get the agglutinated clumps of streptococci into the coronary arteries as directly as possible, the agglutinated suspension was injected directly into the left ventricular cavity shortly after the organisms showed agglutination in the test tube. This proved a satisfactory method, since many clumps of bacteria were found in the small vessels of the heart in animals accidentally dying a few minutes after injection.

Thirty-four rabbits were inoculated intracardially. Each rabbit received about 5 cc. of a suspension of agglutinated streptococci and was given from one to eight injections. Animals were killed or died at intervals of from one to sixty days after the first injection. Myocarditis to some extent occurred in all but one, as shown in the accompanying table. The most constant reaction was proliferative in character, being present in all but one of the thirty-four cases.

The earliest reaction noted was in an animal killed twenty-four hours after its first inoculation. Clumps of bacteria were lodged in the smaller vessels, and polymorphonuclear leukocytes were collected about

8. Clawson, B. J.: Studies on the Etiology of Acute Rheumatic Fever, J. Infect. Dis. **36**:444, 1925.

these clumps outside the vessels. The chief reaction was proliferative in type. The loose connective tissue cells in the interstitial areas near the clumps of bacteria were swollen. The nuclei became vesicular, and some cells were multinucleated and resembled the cells in rheumatic myocarditis. This proliferative type of inflammation in a greater or less degree occurred in a nodular or diffuse arrangement in all but one of the thirty-four rabbits.

Experimental Myocarditis

	Duration, Days	No. of Injections	Exudative	Proliferative	Nodular Proliferative: Aschoff-Like	Nodular Proliferative: Large Elongated	Pericarditis
1	1	1	+	0	0	+	0
2	1	1	+	+	0	0	0
3	1	1	+	+	0	0	0
4	1	1	+	+	0	0	0
5	1	1	+	+	0	0	0
6	2	1	0	+	+	+	0
7	3	1	0	+	+	+	0
8	3	1	0	+	+	+	+
9	3	1	0	+	+	+	+
10	4	1	0	+	+	+	0
11	5	1	0	+	0	+	+
12	5	1	0	+	0	+	0
13	6	2	0	+	0	0	0
14	7	1	0	0	0	0	0
15	7	1	+	+	+	+	0
16	7	2	+	+	0	+	+
17	8	1	0	+	+	+	+
18	8	1	0	+	+	+	0
19	9	2	0	+	0	+	+
20	10	1	0	+	+	+	+
21	10	8	+	+	0	0	+
22	13	2	0	+	+	+	+
23	13	2	0	+	+	0	0
24	13	2	0	+	+	0	0
25	17	3	+	+	+	+	+
26	20	8	0	+	+	+	+
27	23	2	0	+	+	+	+
28	23	2	0	+	+	0	+
29	25	4	+	+	0	+	+
30	30	4	+	+	+	+	+
31	34	4	+	+	+	+	+
32	34	4	+	+	+	+	0
33	36	4	0	+	+	+	+
34	60	8	+	+	+	+	+
—	—	—	—	—	—	—	—
34	..	..	14	32	21	24	18

Typical small nodules situated in the loose interstitial connective tissue, usually in the region of small blood vessels or beneath the endocardium, were commonly found, occurring in twenty of the thirty-four cases (figs. 1 to 3). These nodules were composed of a clump of cells usually but not always surrounding a small necrotic center or a small thrombosed vessel. Many of the cells were fibroblastic in character, with oval vesicular nuclei. There were also large mononuclear cells, lymphocytes and plasma cells. In most of these nodules from one to several multinucleated cells containing vesicular nuclei were present. The arrangement and character of these mononuclear and multinucleated cells were similar to those found in the Aschoff submiliary nodules in human rheumatic myocarditis. When stained with methyl-green pyronin

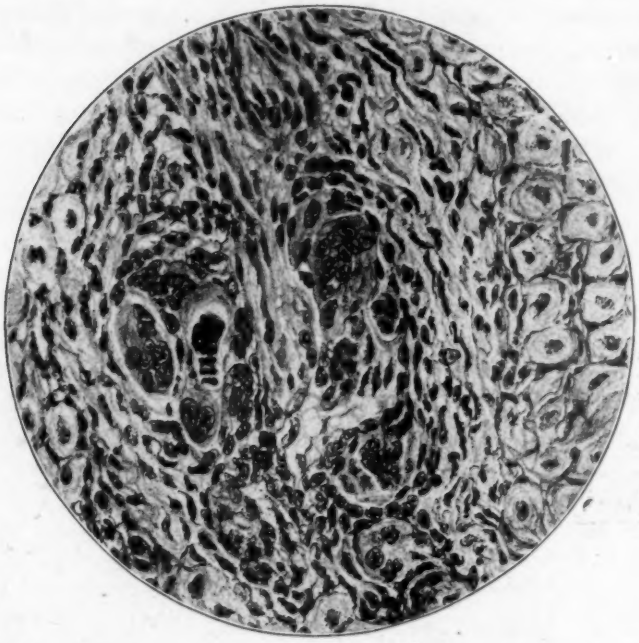

Fig. 1.—A nodular area showing mononuclear cells and giant cells.

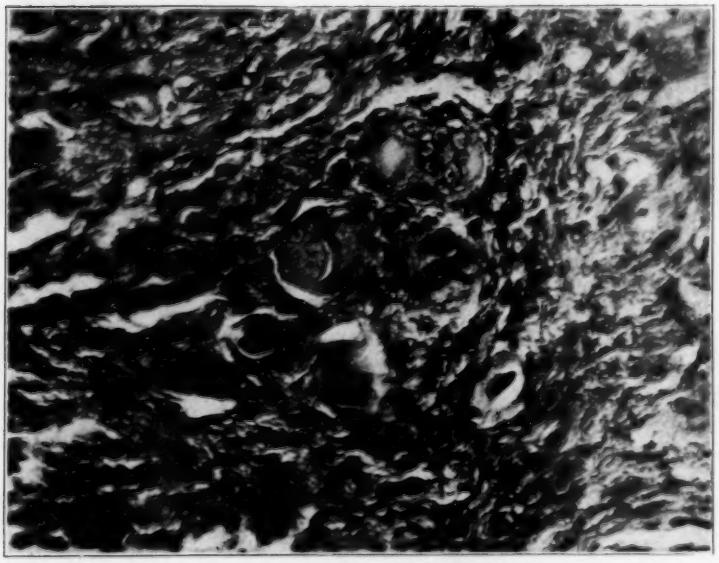

Fig. 2.—An interstitial area showing fibroblasts, mononuclear cells and giant cells.

the cytoplasm took the red stain. Large elongated areas of proliferative inflammation with a similar cellular reaction were present in twenty-four of the thirty-four cases. These elongated areas may correspond to what Aschoff described as extensions of the submiliary nodules in streaks into the surrounding tissues. The diffuse inflammation may be confined to the interstitial areas, or it may gradually replace relatively large areas of muscle.

Many large areas showing various degrees of necrosis surrounded by many fibroblasts, mononuclear and multinucleated cells were to be observed. These necrotic areas appear to result from the lodging of

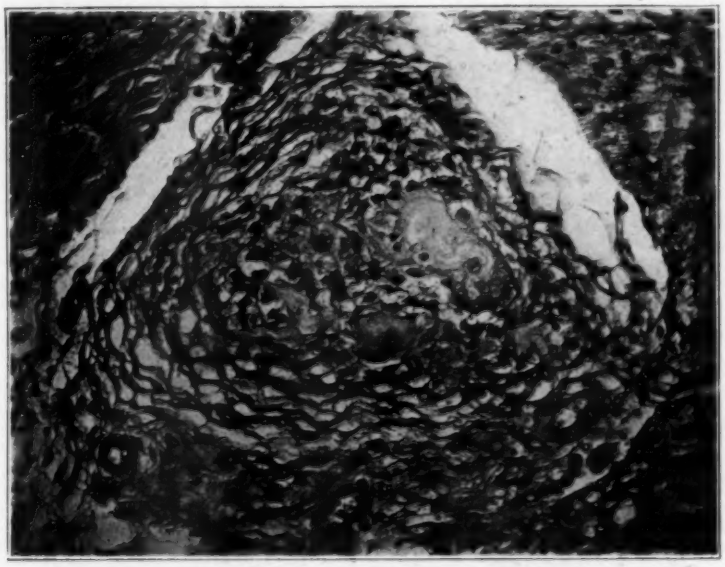

Fig. 3.—A giant cell nodule in loose interstitial tissue.

the larger clumps of streptococci. The character of the reaction about these necrotic centers was similar to the reaction in the nodular proliferative areas.

Another proliferative change noted was the swelling and proliferation of the endothelial cells within the small blood vessels. Sometimes this occurred to such an extent as completely to close the lumen of a vessel (fig. 4). This reaction has been described by Swift [9] as one of the characteristics of rheumatic inflammation. The connective tissue cells within the vessel walls and those immediately surrounding the vessels also exhibited proliferative changes, with swollen cells and nuclei.

9. Swift, H. F.: The Pathogenesis of Rheumatic Fever, J. Exper. Med. **39**:497, 1924.

Exudative inflammation was of less frequent occurrence than the proliferative type. It was present in thirteen of the thirty-four cases, but practically never exhibited extensive involvement (table). As a rule, when present, it occurred as small abscesses, but in one case there was an extensive diffuse exudation of polymorphonuclear leukocytes.

Pericarditis was noted in eighteen of the thirty-four cases (table). All degrees were seen, from a very early beginning to an organized fibrous pericarditis. The cellular exudate was almost entirely composed of macrophages, plasma cells and lymphocytes. Fibrin was present in small quantities. In the pericarditis, as in the myocarditis, proliferation

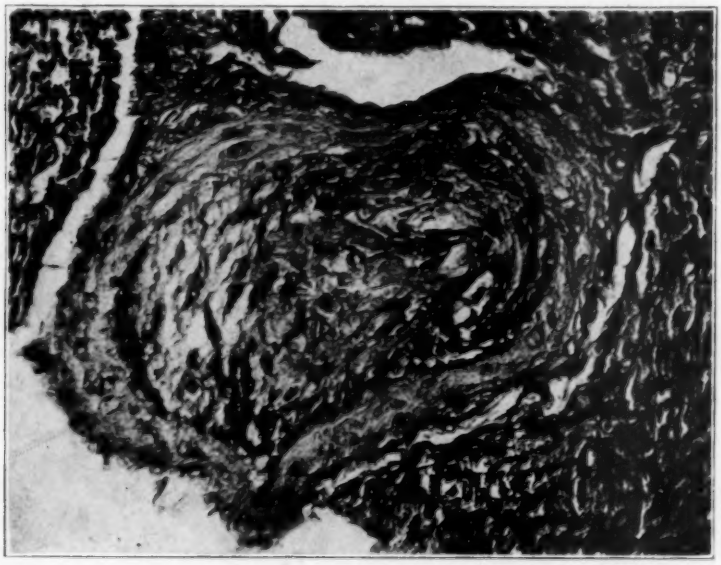

Fig. 4.—Proliferation of endothelial cells to fill lumen of blood vessel.

was pronounced. Many buds of connective tissue could be seen growing between the two layers of pericardium. This experimental pericarditis corresponds closely to that found in rheumatic pericarditis in human cases.

These experiments show that experimental myocarditis and pericarditis are readily produced in rabbits by injecting agglutinated streptococci intracardially. As in human rheumatic myocarditis, the inflammation is located chiefly in the interstitial structures around the blood vessels and in the subendothelial structures. The similarity of the microscopic appearance of human rheumatic and experimental rabbit carditis is pronounced. The inflammation is chiefly proliferative. The exudate is largely mononuclear cells, such as macrophages, plasma cells and lymphocytes. The presence of multinucleated cells with vesicular nuclei is

characteristic in both cases. The staining reaction of the macrophages and multinucleated cells to methyl-green pyronin is similar in both human rheumatic and experimental myocarditis. The great frequency of nodular proliferative inflammatory areas with mononuclear and multinucleated cells in the experimental myocarditis suggests a similarity to human rheumatic myocarditis.

CONCLUSIONS

Myocarditis and pericarditis with a proliferative type of inflammation can be produced in a high percentage of rabbits inoculated intracardially with freshly agglutinated streptococci.

Nodular inflammatory areas showing a cellular reaction similar to that found in human Aschoff bodies are commonly produced in these cases of experimental myocarditis.

PULMONARY EMBOLI IN SUPRARENAL INSUFFICIENCY

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It is the purpose of this paper to record investigations of the histologic changes that occur in suprarenalectomized animals when they are submitted to certain toxic agents. It has been shown that the suprarenalectomized animal reacts fatally to certain agents; namely, bacterial vaccines, that are not harmful to control animals in which at least one suprarenal is present.[1] Observation has demonstrated that the former usually have symptoms of respiratory distress before death. With this in mind, particular emphasis was directed toward an examination of the lungs in the suprarenalectomized animal. At the same time further data were obtained regarding the reaction of the suprarenalectomized animal to egg albumin, dead bacteria and diphtheria toxin.

METHOD

Male rats (*Mus novegicus-albimus*) of a uniform size and type were used.[2] They were kept in separate cages and fed a standard diet, and the room was kept at a constant favorable temperature.[3] After preliminary control observations, all were submitted to operation. At this time both surprarenal glands were removed from the same animals, while in the control animals one suprarenal and a small piece of fat near the other suprarenal were removed. This procedure seemed to submit suprarenalectomized and control animals to as nearly the same amount of trauma as possible.

At stated intervals after operation the agent selected was then injected into the doubly suprarenalectomized and the control rats that had been operated on. In the first series egg white diluted with an equal volume of saline was given intravenously into the femoral vein. Two cubic centimeters of the diluted albumin was the total quantity given each rat. As a check on the effect of injecting intravenously this quantity of fluid in one group of suprarenalectomized rats, each was

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* Presented in abstract before the American Society for Experimental Pathology, Cleveland, Dec. 30, 1925.

1. Scott, W. J. M.: The Toxic Effect of Killed Bacteria in Adrenalectomized Rats, J. Exper. Med. **39**:457, 1924.

2. These rats were all within 25 Gm. in weight of each other.

3. Scott, W. J. M.: The Susceptibility of Adrenalectomized Rats to Morphine, J. Exper. Med. **38**:543, 1923.

given 2 cc. of saline in the same manner. In another series, diphtheria toxin was administered subcutaneously, and in still another series a suspension of killed *Staphylococcus aureus* (1 billion per cubic centimeter) was given intraperitoneally in 5 cc. amounts daily, beginning four weeks after operation. In each group the control animals were killed after injection, at intervals corresponding to the time at which the suprarenalectomized animals were killed by the agents or for experimental purposes. Tissues were fixed immediately in Zenker's solution and in 10 per cent formalin, embedded in paraffin and stained with hematoxylin and eosin. Special stains were also used for particular purposes as referred to later.

PRESENTATION OF DATA

Egg Albumin.—In the first group of lungs examined, a striking phenomenon was noted in the suprarenalectomized rats that had died after the intravenous injection of egg albumin. In some of these lungs, small vessels were found completely plugged with a mass of closely packed cells. No such condition was found in the singly suprarenalectomized animals receiving injections in the same manner.

The phenomenon in its complete form consists in a filling of the lumen of a small pulmonary vessel with mononuclear cells. Both pulmonary arterioles and venules may be involved. This was verified by the staining of the elastic fibers of the affected vessels (Weigert's stain). It is impossible to make a positive statement about the condition of the capillaries, but in several instances they were much thicker, and had many more nuclei, than normal. It is our opinion that they also were filled with the same type of cells.

The plugged vessels were filled with cells of the large mononuclear type. Their nuclei stained deeply with hematoxylin and were hyperchromatic. About half of the nuclei were indented. The cytoplasm was pale bluish pink. These cells were not differentiated by vital dyes.

In some lungs several good examples of the plugged vessels occurred in one low power field, while in others it was necessary to search through several fields in order to find an instance of the complete form.

Other vessels, more numerous than the foregoing, showed the partial form of the phenomenon. The vessels were filled with the same type of cells mixed with some red cells and serum, or were only partially occluded by the mass of mononuclear cells. The large pulmonary arteries and veins were not affected by the process.

Seventeen doubly suprarenalectomized rats were given intravenously 1 cc. of egg albumin diluted with an equal volume of saline (see table). Of these, nine, or 53 per cent, had definite cellular emboli of this type. These were produced by the injection of egg albumin at the end of one week, two weeks and three weeks after operation. The emboli were not seen in the animals treated in the same manner four weeks after operation.

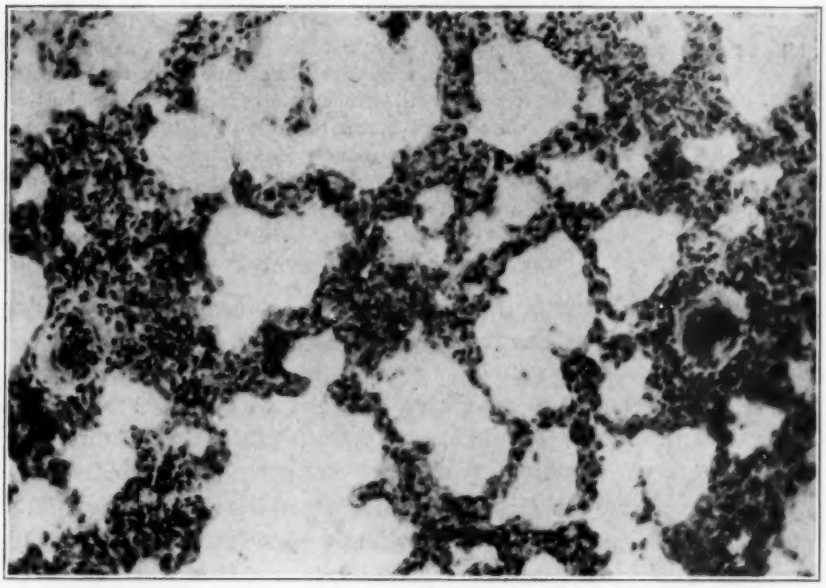

Fig. 1.—Two pulmonary arterioles in the same section plugged with mononuclear cells. Egg albumin was injected intravenously fourteen days after double suprarenalectomy. Low power magnification.

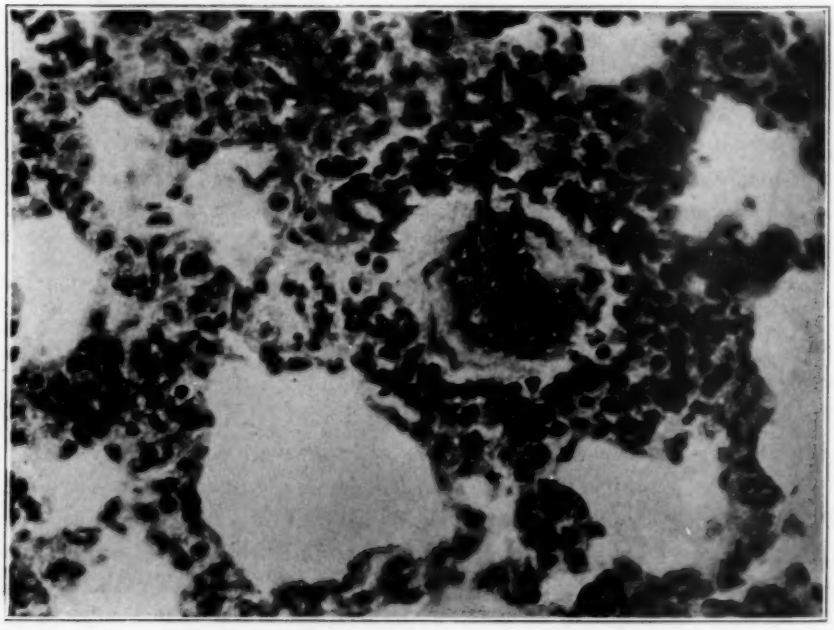

Fig. 2.—High power magnification of a plugged arteriole.

Other Lethal Agents.—To determine whether these cellular emboli were associated specifically with egg albumin, the lungs of suprarenalectomized rats were studied after the employment of other lethal agents. In the first place, in the course of this and some other work, twenty-three rats died or were killed from one to twenty-eight days after double suprarenalectomy. Six of these, or 26 per cent, showed the same type of cellular plugs in the smaller pulmonary vessels that had been found in the doubly suprarenalectomized animals after the injection of egg albumin.

Another series of five rats received daily injections intraperitoneally with 5 cc. of killed *Staphylococcus aureus* suspension (one billion per cubic centimeter) beginning twenty-eight days after operation. Three of these were doubly suprarenalectomized, and two singly suprarenalectomized. The three doubly suprarenalectomized rats died in from ten to sixteen days; the singly suprarenalectomized animals survived. After the injections had been continued for eighteen days, the animals were killed. One of the doubly suprarenalectomized rats showed cellular emboli of exactly the same type as that found after egg albumin. Both of the controls that had been operated on had normal lungs.

In the same manner, 2 cc. of diphtheria toxin was injected subcutaneously, seventeen days after operation, into a group of six doubly suprarenalectomized rats. All of the doubly suprarenalectomized rats died within eighteen hours, and both of the controls that had been operated on survived and were killed fourteen days later. In none of these animals were the cellular emboli found.

Control Procedures.—(*a*) Single suprarenalectomy: Thirteen rats were operated on in the same manner as those described in the foregoing, except that only the right suprarenal was removed, leaving the left suprarenal with its blood supply intact. A corresponding amount of trauma on the left side was inflicted by removing a piece of fat immediately above the left suprarenal. These singly suprarenalectomized rats received injections with egg albumin in the same amounts and at the same intervals after operation, and were killed at corresponding intervals after injection. Twelve of these thirteen had no abnormalities of the pulmonary vessels. One showed the same phenomenon as had been observed in the doubly suprarenalectomized animals. In this case, however, the spleen had been injured; its distal third was necrotic and surrounded by a large intra-abdominal abscess. This was the only instance of abscess in either singly or doubly suprarenalectomized rats. Unfortunately, frozen sections of the remaining suprarenal were not obtained, but from the known effect of bacterial intoxications on the suprarenal cortex, it is our belief that this animal had a serious impairment of the

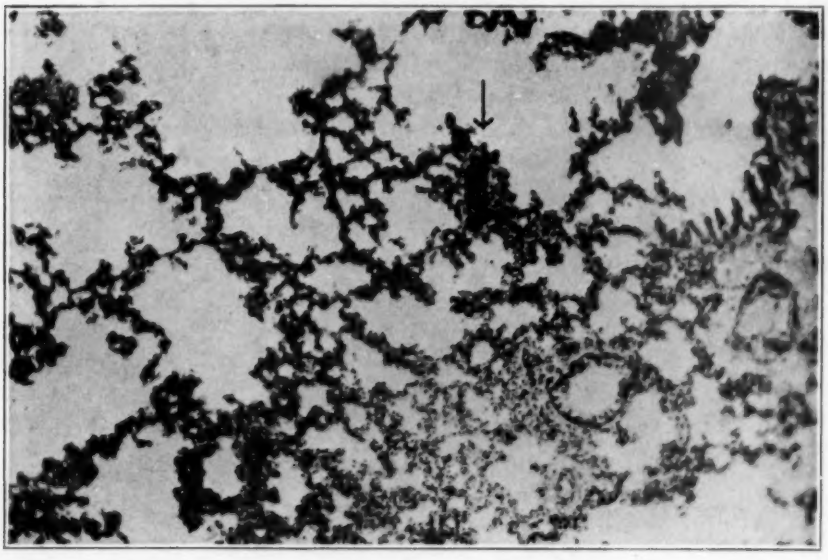

Fig. 3.—Pulmonary venule filled with mass of mononuclear cells; low power magnification.

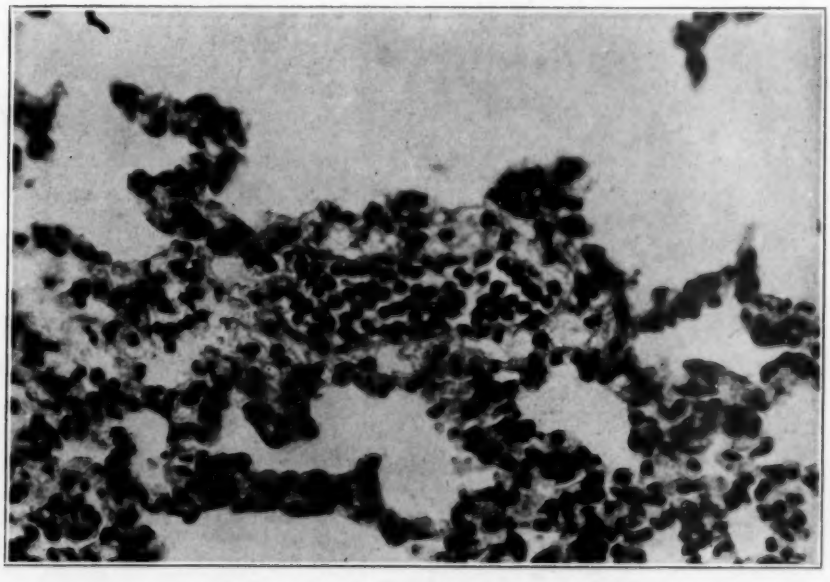

Fig. 4.—High power magnification of a similar venule.

cortical function of the remaining suprarenal. This rat showing cellular pulmonary emboli represented 8 per cent of the singly suprarenalectomized animals.

(*b*) Intravenous Saline: In order to control further the occurrence of these cellular emboli, nine doubly suprarenalectomized rats received intravenous injections with 2 cc. of saline. This was done from fourteen to sixteen days after operation, as it was at this interval that the best plugging of the vessels was found. These animals were killed two, four and twelve hours after injection. In none of them was any abnormality of the pulmonary vessels found. The lungs of three normal rats from the same lot, killed with ether, showed normal pulmonary vessels.

COMMENT

When these masses of cells, filling the smaller pulmonary vessels, were first seen, we thought them to be thrombi formed in situ. On the application of special stains, however, fibrin was not found to be present (Weigert's differential stain and Mallory's chloride of iron hematoxylin stain) and no platelets could be observed (Wright's method). Consequently, it does not seem justifiable to call them thrombi. On the other hand, the occlusion by the masses of cells of both venules and arterioles would make it appear that the latter were formed in situ by the conglutination of these mononuclear cells. As we lacked a term to designate more exactly this local conglutination, we have called these intravascular cellular masses emboli. No preformed thrombi of such cells were found in any other organ.

The production of cellular plugs in the pulmonary vessels of suprarenal deficient animals has not, so far as we know, previously been reported. Marine [4] and his associates, however, have called attention to the fact that after sufficient but sublethal injury to the suprarenal glands, the lymphoid tissues undergo hypertrophy. It may be that the mononuclear cells forming the pulmonary plugs are related to this lymphoid stimulation.

The origin of the mononuclear cells is not accurately known. No evidence of phagocytosis was seen in them, but the cells were so closely packed that this would have been extremely difficult to make out. By the repeated intravenous injection of colloidal dyes, Simpson [5] produced showers of macrophages appearing in the right ventricular blood, and largely filtered out of the blood in the passage through the lungs. She reported a plugging of the pulmonary capillaries with macrophages dur-

4. Marine, D.; Manley, O. T., and Baumann, E. J.: The Influence of Thyroidectomy, Gonadectomy, Suprarenalectomy and Splenectomy on the Thymus Gland, J. Exper. Med. **40**:249, 1924.

5. Simpson, M. E.: The Experimental Production of Macrophages in the Circulating Blood, J. M. Res. **43**:77, 1922.

ing the showers. The phenomenon which we have observed in suprarenalectomized animals may be related to these macrophage showers, and this is suggested by the fact that although seen both in pulmonary venules and arterioles, no such plugs were seen in other organs. It may be that the single injection of the colloid will suffice to produce a macrophage shower in suprarenal deficient animals. This phase of the subject is being investigated further.

A marked concentration of the blood following double suprarenalectomy has been reported. It appears highly unlikely that the concentration of blood can be the cause of the phenomenon observed by us. In the first place, the concentration of the blood is reported in animals dying from the effects of suprarenal extirpation, not in rats surviving in good condition three weeks after operation. If the cellular plugs in the small pulmonary vessels were dependent on some general alteration in the characteristics of the blood, we should expect to find such masses of cells in the vessels of other organs. The latter is not observed. It seems probable that the phenomenon observed by us is due to the outpouring of mononuclear cells somewhere in the systematic circulation which are then swept into the pulmonary vessels, and are held there by conglutination and filtration.

The occlusion of the smaller pulmonary vessels was not the direct cause of death. This seems clear as several of the suprarenalectomized rats which were killed by the egg albumin did not show the emboli in the few sections examined, while another that was killed showed numerous occluded vessels.

The present study did not have as its object the determination of the resistance of suprarenalectomized rats to intoxications. It has been previously reported by one of us that for several weeks after operation intoxication with killed bacteria (in the proper dosage) will prove invariably fatal to suprarenalectomized rats, while it is harmless for the controls that have been operated on.[1] In the present study further confirmation of this was obtained in the series receiving daily injections with *Staphylococcus aureus* vaccine. Three doubly suprarenalectomized, and two control rats, that had been operated on, were in good condition four weeks after operation. Daily intraperitoneal injections of the suspension of killed bacteria was then begun. After fifteen days, all of the suprarenalectomized animals had died. The controls were killed in good condition two days subsequently.

Certain accessory data in regard to the toxicity of egg albumin in suprarenalectomized animals, and of diphtheria toxin, were obtained. Twenty-one doubly suprarenalectomized rats in excellent condition received intravenous injections with 2 cc. of an equal mixture of fresh egg white and saline solution. The interval after operation varied from

seven to twenty-eight days. Of these twenty, or 95 per cent, died within eighteen hours, most of them within five hours. Fourteen singly suprarenalectomized rats at the same interval after operation were given the same mixture intravenously. Of these only one (or 7 per cent) was killed by it. The intravenous injection of 2 cc. of fluid was not the cause of death. This was determined in nine doubly suprarenalectomized rats receiving intravenous injections with 2 cc. of saline solution fatal in no instance.

Results of Intravenous Injection of 2 cc. of 50 Per Cent Egg White Into Suprarenalectomized Animals

Operation	Interval After Operation, Days	Results	Microscopic
Double suprarenalectomy	7	Died in 4 hours	Plugs
	7	Killed in 3½ hours	Numerous plugs
	14	Died in 2½ hours	Plugs
	14	Died in 3½ hours	Plugs
	15	Died in 2½ hours	Plugs
	16	Died in 40 minutes	No plugs
	16	Died in 40 minutes	No plugs
	16	Died in 10 minutes	No plugs
	21	Died in 2½ hours	Plugs
	21	Died in 2½ hours	Occasional plugs
	21	Died in 1 hour	Occasional plugs
	21	Died in 17 hours	No plugs
	21	Died in 2 hours	Plugs
	29	Died in 30 minutes	No plugs
	29	Died in 1½ hours	No plugs
	29	Died in 1½ hours	No plugs
	29	Died in 1 hour	No plugs
Simple suprarenalectomy	7	Killed in 4 hours	No plugs
	7	Killed in 4 hours	No plugs
	7	Died in 3 hours	No plugs
	7	Killed in 3 hours	No plugs
	15	Killed in 3 hours	Plugs; abdominal abscess with necrosis of spleen
	15	Killed in 4 hours	No plugs
	15	Killed in 5 hours	No plugs
	16	Killed in 1 hour	No plugs
	16	Killed in 1 hour	No plugs
	21	Killed in 18 hours	No plugs
	29	Killed in 2 hours	No plugs
	29	Killed in 2 hours	No plugs
	29	Killed in 4 hours	No plugs

Diphtheria toxin was injected in amounts of 1 and 2 cc. (L + = 0.53 cc.) in eleven doubly suprarenalectomized rats, and two controls that had been operated on. In every instance the former died, usually within twelve hours; the control animals were killed in good condition fourteen days after injection. Whether the effect, however, was due to the diphtheria toxin alone is doubtful, as in two cases 1 cc. of antitoxin injected at the same time as the diphtheria toxin proved fatal to suprarenalectomized rats. The latter result may be due to the horse serum of the antitoxin. Further work on this subject is contemplated.[6]

6. The diphtheria toxin was the concentrated toxin obtained from Parke, Davis & Co.

CONCLUSIONS

Plugs of mononuclear cells are frequently found in the smaller pulmonary vessels of suprarenal deficient rats after a single intravenous injection of egg albumin; also in chronic intoxication with dead bacteria and in fatal suprarenal insufficiency.

This phenomenon presents evidence of an unusual stimulation of some mononuclear cellular system, whether lymphatic or endothelial has not been determined.

Accessory data are presented bearing on the diminished resistance of suprarenalectomized rats to (*a*) egg white injected intravenously, (*b*) chronic intoxication with *Staphylococcus aureus* and (*c*) diphtheria toxin.

SUPRAVITAL REACTION TO NEUTRAL RED OF THE CELLS OF LYMPH NODES OF HODGKIN'S DISEASE *

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The large mononuclear and multinuclear cells with vesicular nuclei containing one or more nucleoli are the characteristic histologic feature of Hodgkin's disease of lymph nodes whether the node be the soft cellular one of the early stage or the hard fibrous one of the later stage. These cells may be less abundant than other types of cells such as the lymphocytes, but in them mitoses may usually be found and not infrequently multipolar mitoses. Different views as to the origin of these cells are: first, that they are of lymphoblastic origin; second, that they are derived from the reticulo-endothelium; and third, that they are of a reticular type but arise not from the reticulo-endothelium but from a stem cell in common with the lymphocytes. The living reticulo-endothelium of lymph nodes when brought into contact with solutions of neutral red reacts in a characteristic fashion with the formation of spherical aggregations of the dye granules in the cytoplasm.[1] Through the cooperation of the Department of Surgery, Washington University School of Medicine, St. Louis, a lymph node was obtained, by biopsy, from a case of Hodgkin's disease, and within five minutes treated with neutral red for the purpose of comparing the reactions of the various cells present with those of the cells of the normal lymph node.

REPORT OF A CASE

History.—S. P. D., a man, aged 34, a car-repairer, was admitted to the Barnes Hospital on June 3, 1926, complaining of exhaustion and a lump in the neck. He had had a chancre twelve years ago, and had been treated with arsphenamine and mercury. About two years ago, he noticed diffuse enlargement in the region of the thyroid and smaller lumps above the clavicles, which were slightly tender. In December, 1925, he caught cold, and the lumps above the clavicles increased in size. The cold was accompanied by a nonproductive cough and night sweats.

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* From the Department of Pathology, Washington University School of Medicine.

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Physical Examination.—Bilaterally just above the clavicle, discrete, firm nodules were felt. The largest masses were about 5 cm. in diameter. Similar masses were present in both axillae. The temperature was 38.8 C. (101.8 F.) at 8 p. m. on June 3. Blood examination revealed: white cells, 20,800; differential count: polymorphonuclear neutrophils, 87 per cent; lymphocytes, 3 per cent; transitionals, 10 per cent; red cells, 3,560,000; hemoglobin, 40 per cent.

Clinical Diagnosis.—Hodgkin's disease.

At biopsy on June 4 a supraclavicular lymph node measuring 1.5 cm. was removed. Within an intact capsule the tissue appeared moderately firm. The cut surface showed areas of semitranslucent cellular tissue with grayish firm tissue elsewhere.

Histologic Diagnosis.—Hodgkin's disease.

Method.—After fixation of a small piece of the node in Zenker's solution for routine diagnosis, the remainder was at once injected with physiologic sodium chloride saturated with neutral red (Gruebler) by a method [1] which had previously been found to give good results with normal lymph nodes. By means of a syringe and small needle the dye solution was forced out into the tissue at a dozen different places using the necessary pressure. About 5 cc. of the solution was forced into the node in this way with much of it escaping through the cut capsule and the vessels. After thorough injection, the tissue was kept at room temperature in saline solution for forty-five minutes, when it was transferred to a mixture of 15 parts of formol and 85 parts of Zenker's solution without acetic acid. After from twelve to eighteen hours, it was transferred to Zenker's solution without acetic acid for twelve hours. It was then cut into blocks from 2 to 3 mm. thick for paraffin embedding as follows: acetone (two changes) for one hour, benzol twenty minutes, melted paraffin twenty minutes. Sections 5 microns thick were cut and attached to slides with albumin fixative by allowing them to dry for twenty-four hours at room temperature.

Staining.—After removing all paraffin about the sections, the paraffin was removed from the tissue by placing the slide for two minutes in benzol. The slide was removed from the benzol, and at the moment the preparation whitened it was plunged for five seconds into a jar of hematoxylin (Harris without acetic acid), washed for one second and plunged for one second into an upright staining jar containing acetone. It was then cleared in xylol and mounted in balsam. The slide was rapidly agitated in all the solutions. The hematoxylin acted best when new.

Results.—Sections from the five blocks showed areas that had reacted supravitally. As usual the penetration was irregular with the reacting cells at the periphery of heavily colored foci in which the dye concentration and the mechanical damage had brought about extensive cell death. Although there were present in the cytoplasm of lymphocytes from two to five very minute granules when the individual cells in the blood or in the exudates of animals were brought into contact with the dye and examined fresh without fixation, the lymphocytes never contained dye granules after embedding. The granules of eosinophils retained the red color tenaciously and were intensely stained in the sections. Cells which had the structure of typical fibroblasts might contain a few scattered dye granules, but these granules were not grouped in a focus.

Large Mononuclear and Multinuclear Cells.—In size, shape and nuclear character the remaining cells were variable, but the reaction of this group of cells to supravital neutral red indicated that they were of the same type. The smallest

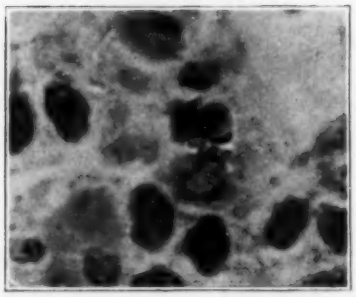

Fig. 1.—Small cell only a half larger than lymphocytes. A small group of dye granules in cytoplasm above the vesicular nucleus. In this and the following illustrations, the photographs were taken with 3 mm. Zeiss apochromatic objective, No. III, Homal Zeiss ocular and a bellows length of 250 to 350 mm. In all sections the dye granules were a bright red with nuclei and cytoplasm faintly colored with hematoxylin.

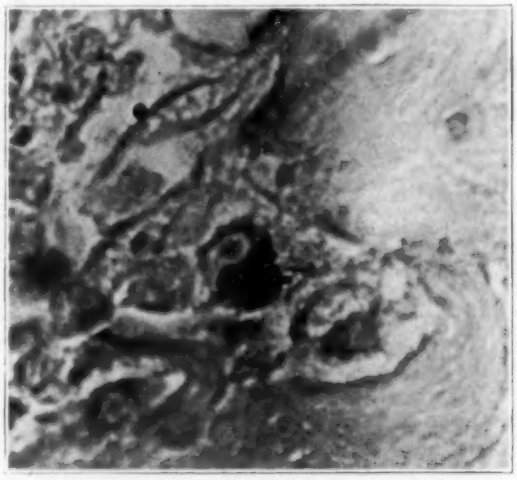

Fig. 2.—Two cells with dye foci in a part of the section with much hyalinized collagen.

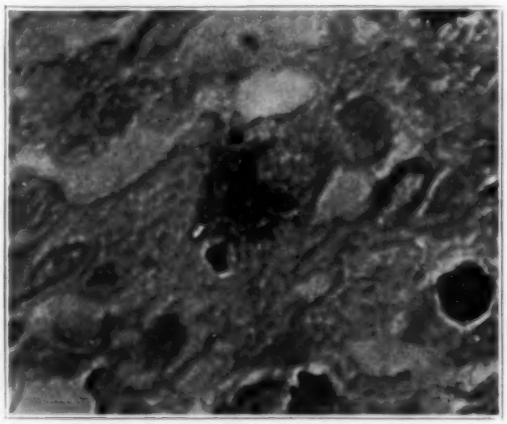

Fig. 3.—Large cell connecting with others. The large mass of dye granules is in contact with one side of the nucleus.

cells of this type were twice the size of lymphocytes. Unlike lymphocytes, most of them were connected by reticular processes. In an occasional cell there was a small focus of dye granules (fig. 1). In sections, only the heavier dye foci and the large granules were preserved. In this connection it must be kept in mind that the central, smaller dye granules of a spherule may be lost and the large

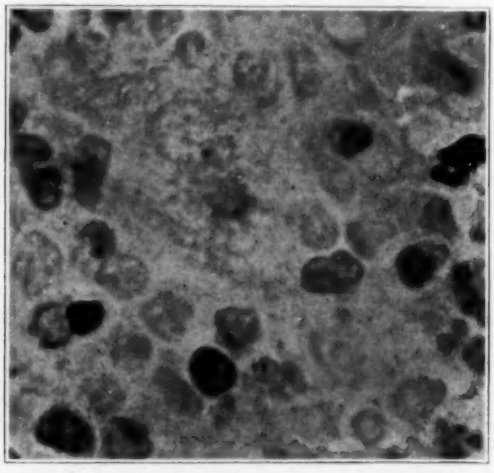

Fig. 4.—Large cell with single light nucleus and abundant very light cytoplasm in which the dye granules are arranged in wreath form.

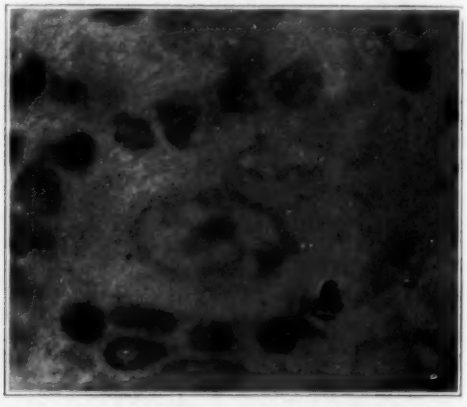

Fig. 5.—Cytoplasm of this large cell is indicated by the nuclei of the small cells that surround it. At one of the ends of the large cupped nucleus there is a small mass of neutral red granules.

and somewhat scattered granules at the periphery preserved. In such cells it appears on first inspection that the granules are diffusely distributed. The larger cells may contain a large, and often quite round, nucleus with scant cytoplasm. The dye focus in such cells is small, but owing to the bright red color of the granules, it is distinct. In some instances the dye foci of medium-sized cells was very heavy (fig. 2). In large cells with abundant cytoplasm very large dye foci

occurred (fig. 3). Such cells were often distinctly reticular in the sense that they connected with other cells by branches. Occasionally the wreath appearance seen so well in the fresh unfixed tissues was present in the sections (fig. 4). In places in the sections the cytoplasm of such large cells was homogenous and had much the appearance of hyalinized collagen. The other variations in structure

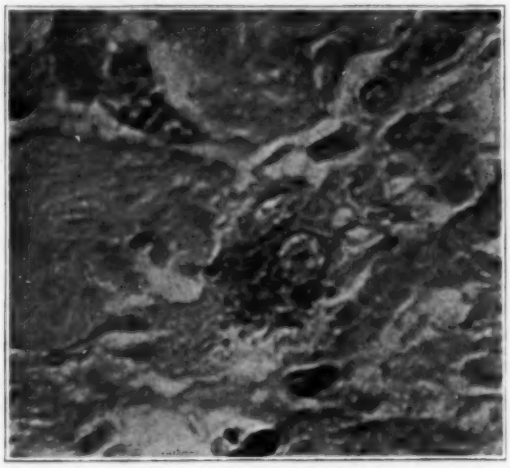

Fig. 6.—Two foci of dye granules in two cells or in a double nucleated cell.

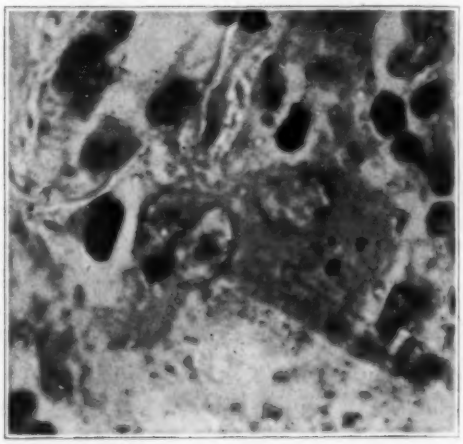

Fig. 7.—Multinucleated cell with one large neutral red granule about which there are smaller less distinct ones.

were due to nuclear changes. Very large, round, hyperchromatic nuclei sometimes almost completely filled the cell, but often the large nucleus was irregular in outline and not infrequently quite polymorphous (fig. 5). In either case the spherical mass of neutral red was smaller than in the cells with abundant cytoplasm. There were multinucleated cells of the typical Langhan's type, but of thsee there were relatively few. In figure 6, there are two cells side by side, each

with its spherule of neutral red. It was not possible to determine in this instance whether the two formed a single syncytial mass. As many as five cells with five neutral red spherules grouped in this way were seen. However, in a great majority of the multinucleated cells there was a single neutral red focus (fig. 7). The cells on the whole had relatively large nuclei. The focus of dye was about proportional to the quantity of cytoplasm, which means that the mass of dye granules was usually not so large as in epitheliod cells of tubercles of the same size.

SUMMARY

The large mononucleated and multinucleated cells of a typical Hodgkin's disease lymph node react supravitally to dilute solutions of neutral red with the formation in the cytoplasm of spherical masses of dye granules. The structural variations in them and in related kinds of cells is great. Thus in tuberculosis the epithelioid and giant cells are characterized by abundant cytoplasm. In Hodgkin's disease the nucleus of this type of cell tends to be large, hyperchromatic and often irregular in shape. These characters considered in connection with the abundant mitoses indicate a local active proliferative process rather than an accumulation of migrated cells formed elsewhere. A majority of these cells are connected by cytoplasmic prolongations, but many possess no reticular processes. If one compares the cells with epithelioid cells of tubercles of the same size, the cytoplasm of the latter is found to be relatively large, and in general the size of the mass of dye granules is proportional to the amount of cytoplasm. Of course many cells are present in Hodgkin's tissue which are exactly like the epithelioid cells of tubercles, but as a whole there is a difference which is explained by the rapid proliferation by mitosis of the Hodgkin's tissue cells.

By the method employed by us, the typical dye focus is preserved only in comparatively few cells. This is due to the removal during the preparation of the sections of much of the dye from the cells in which it is slightly mordanted by the fixation. Also as the dye penetrates the tissue the concentration is correct for the reaction only in certain areas. In all sections from the five blocks, however, there are cells that represent the varied forms of this group which react with the formation of a single focus of dye granules. These cells in their reaction to the dye are like the reticulo-endothelium of lymph nodes, and especially like the hypertrophied reticulo-endothelial cells which have been stimulated by experimental means. After an examination of normal, hypertrophied and tuberculous lymph nodes by the supravital method, it is yet uncertain whether both lymphoblastic cells and reticulo-endothelial cells may arise from a common less differentiated cell, but no evidence has been obtained to support the view that these two types of cells are related. In their reaction to neutral red the two appear to be entirely distinct. A study of the sections was not helpful either in establishing or in disproving a

relationship between these cells reacting with single foci of dye granules and collagen-producing fibroblasts. Elsewhere evidence has been presented which tends to show that the two types are unrelated.[2] However, the two kinds of tissue, reticular and fibrous, may without doubt resemble each other in sections stained by the usual methods, since numerous fibrils are present in both.

CONCLUSIONS

The supravital reaction to neutral red of the large cells of Hodgkin's tissue is like that of the reticulo-endothelium of normal and hypertrophied lymph nodes.

The characteristic large mononuclear and multinuclear cells of Hodgkin's disease are derived from the reticulo-endothelium of the type found in lymph nodes.

The large hyperchromatic nucleus with a relatively small cytoplasmic mass of dye granules points to a local multiplication by mitosis which is rapid in comparison with that of the same kind of cell in epithelioid tubercles.

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2. McJunkin, F. A. (footnote 1, third reference).

MALIGNANT TUMOR OF THE THYMIC REGION

WITH EXTENSIVE METASTASES *

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Recently several cases of tumors in the thymic region have been reported, the term thymoma often being used in classifying them although their histology varied considerably. That a more exact determination of these tumors from the standpoint of their histogenesis is advisable, is illustrated by a case which we have lately had occasion to observe in our laboratory.

REPORT OF CASE

History.—A white man, aged 36, was admitted to the Research Hospital of the University of Illinois with the following symptoms: swelling of the neck, feeling of pressure in the chest, cough, dyspnea, loss of voice, night sweats and loss of weight (50 pounds, 22.7 Kg., in five weeks). The patient had been perfectly well until five weeks before admittance to the hospital when these symptoms developed. The remaining history was unimportant except for an operation on the thyroid gland fifteen years ago.

Physical Examination.—The patient was poorly nourished, anemic and very dyspneic. He had an enormous swelling of the neck, edema of the face and dilation of the superficial veins of the chest and abdomen. The lymph glands of the neck were enlarged, hard, matted together and fixed to the cervical structures. The thyroid gland was slightly enlarged and very hard. The substernal dulness was increased, measuring 8 cm. to the right of the midsternal line and 6 cm. to the left.

Blood count revealed: hemoglobin, 75 per cent; red blood cells, 3,600,000; white blood cells, 5,200; differential count: polymorphonuclears, 80 per cent; lymphocytes, 16 per cent; mononuclears, 4 per cent; platelets, 300,000. Urinalysis revealed a 2 mm. ring of albumin and no casts. The Wassermann test was negative. Chemical examination showed that the blood was normal.

Fluoroscopic and roentgen-ray examinations revealed a broad mediastinal shadow and bilateral hydrothorax.

Since the clinical examination of the thyroid gland revealed a swelling of this organ, a tentative diagnosis of carcinoma of the thyroid was made, and a small biopsy specimen was removed. The pathologic diagnosis was a malignant tumor of the thyroid gland.

Pathologic Report (Necropsy by Dr. R. H. Jaffé).—The dead body was that of a well developed, poorly nourished, very pale, white man about 40 years of age. The superficial veins of the chest and abdomen were dilated. The face was edematous, the neck deformed, the deformity being due to a hard lobulated mass on either side beneath the edematous subcutaneous tissue. An old thyroidectomy scar was present.

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The peritoneal cavity contained no free fluid; the diaphragm was pushed down on either side of the sixth rib. The liver edge was 15 cm. down from the costal margin in the right midclavicular line. A large firm lobulated retroperitoneal mass was felt in the region of the pancreas.

On removing the sternum, a tumor growth was exposed in the anterior superior mediastinum which was firmly attached to but did not infiltrate the bone. The growth was 10 cm. across, roughly pyramidal in outline, extending upward almost to the thyroid gland and downward infiltrating the heart and pericardium. The hilum surfaces of the lungs were firmly attached to the mass. On section this tumor was homogenous and grayish white throughout.

The pericardial cavity was obliterated by the infiltrating tumor tissue. The walls of the auricles were almost completely replaced by tumor; the fibrous ring of the mitral valve was from 2 to 3 cm. thick with tumor tissue.

Each pleural cavity contained approximately 1,000 cc. of a light straw colored fluid. In the visceral pluera of each lung were numerous grayish white flat plaques extending from 2 to 3 mm. into the lung tissue. Between these plaques was a network of fine white lines which appeared to be dilated lymph vessels. On section the tumor was found to infiltrate the lungs near the hilum surfaces. In the lower part of the right lower lobe were numerous red, granular, raised, solid areas.

The thyroid gland was enlarged, hard and firmly attached to the overlying muscles and compressed the trachea. On section it was found that the entire gland was replaced by white homogenous tissue except for an area 1 cm. across in the center of the left lobe which resembled normal thyroid tissue.

The lymph glands of the neck were enlarged, quite firm, white and homogenous. On either side they formed a continuous chain reaching to the angle of the jaw, surrounding but not infiltrating the great vessels.

The superior and the inferior venae cavae were compressed by tumor, but everywhere their lumina were free from newgrowth or antemortem thrombi.

The pancreas weighed 214 Gm. and was completely replaced by tumor. In the tail of the pancreas was a dark red, spherical nodule 6 mm. in diameter, resembling splenic tissue.

The kidneys were greatly enlarged by the numerous tumor nodules varying from 1 to 4 cm. in diameter. The right kidney weighed 780 Gm. and the left 465 Gm.

The liver weighed 1,500 Gm. and had the normal acinar structure on section except near the outer surface of the right lobe, where there was a flat, white tumor mass 5 cm. in diameter in the capsule, infiltrating the liver for a distance of 1 cm.

The left suprarenal was compressed by tumor tissue while the right was infiltrated by it.

The linings of the aorta, the gastro-intestinal tract and the bladder were normal; the prostate and the testicles were unchanged.

The skull was not opened.

Microscopic Report.——Under the lower power magnification the tumor appeared as a solid mass of cells, closely packed together and separated into irregular areas only by the preexistant trabecular reticular and septal structures of the affected organ. High power magnification showed the cells arranged into minute alveoli which were surrounded by thin walled capillaries and finest reticular fibers usually stained black with the Maresch Bielschowsky method. In some places also purple stained fibers were discernible in the perialveolar septums.

Although the tumor revealed a great variability as to size, shape and structure of the composing cells, the unit of the newgrowth may be described as follows: a large cell with a very delicate cytoplasm stained pale purple with hemalaum eosin. The outlines of the cells were not distinct, because the cytoplasm formed branches which were so fine that very thin sections only made them visible. These branches connected the cells with each other and also seemed to extend into the perialveolar septums. The nucleus was large, occupied much of the cell body and sometimes was surrounded by a very thin protoplasmic belt. The basal structure of the nucleus was oval, but this structure was rarely found. Deep indentations caused the nucleus to assume very irregular outlines, and no two nuclei

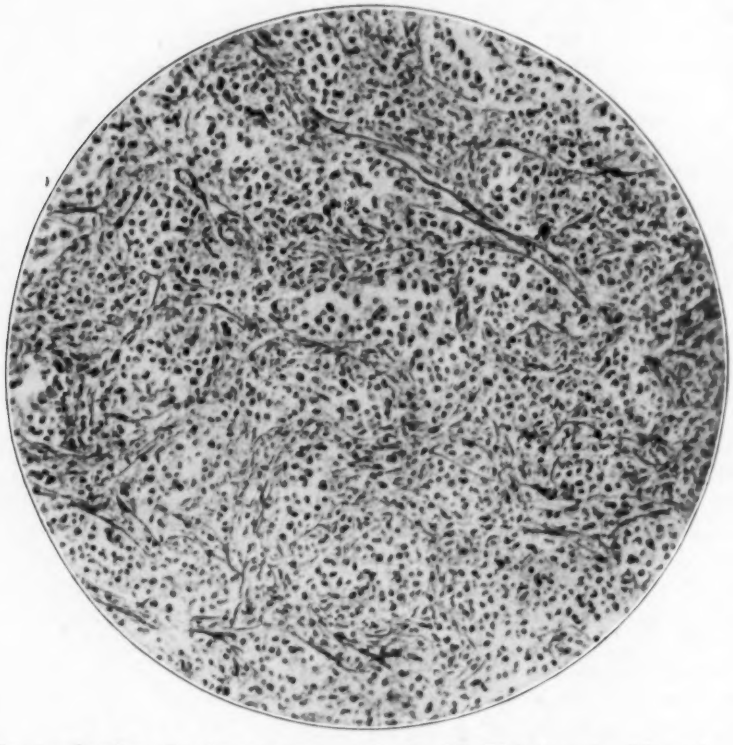

Fig. 1.—Section of primary tumor stained with Bielschowsky Maresch silver impregnation stain for the distribution of the fibrillar connective tissue; × 135.

were alike. The chromatin was relatively scanty; it formed granules which accumulated near the membrane so that the central parts were clear and almost empty. A few nuclei had large oxyphilic nucleoli. Here and there a single very large cell with several darker nuclei and a more hyalinic protoplasm was seen.

Mitotic figures were numerous. The chromosomes were short and clumsy, often packed together into a deeply stained solid mass.

The tumor cells showed little tendency to undergo regressive changes. In a few places only were the cells filled with fat droplets. Necrosis was not observed.

The blood vessels although frequently embedded in tumor tissue were not infiltrated by the tumor cells. Where single cells invade the adventitia, they seemed to shrink and to become surrounded by hyaline tissue.

The tumor of the mediastinum contained a large amount of hyaline connective tissue which in the form of a thick trabecular framework surrounded small nests of tumor cells. In some places also single tumor cells seemed to become isolated by the hyaline stroma. Finally, there were areas composed of only connective tissue. The tumor cells did not differ from the description above. The branching cytoplasm was very distinct, perhaps more distinct than in the metastases. The large nuclei with their clear centers often contained several large oxyphilic nucleoli. Besides the large tumor cells, smaller ones somewhat resembling lymphocytes were observed. Their number was small as compared to the large cells.

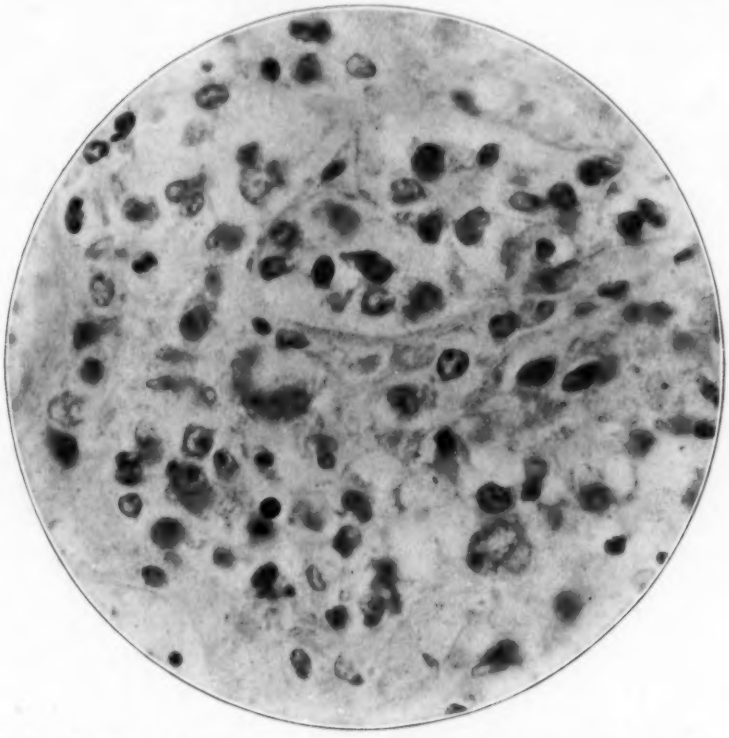

Fig. 2.—Section of the primary tumor showing the arrangement of cells about small alveoli, the great variation in the nuclei and the branching of the cytoplasm; × 560.

In the lung and pleura, the tumor cells were located in the lymph vessels and were closely packed together, cell bordering on cell. There was no separating fibrillar material visible between the cells. Where the cells broke through the walls of the lymphatics and invaded the surrounding tissue they mingled with the connective tissue, and small groups of cells or single cells thus became isolated. Similar observations were made in the alveoli; many alveoli were filled with tumor cells. Here also the cells formed solid masses and seemed not to be interlaced with fibers. Besides the tumor cells, large cells with a vacuolated ample cytoplasm were found. These cells contained coal pigment. Their cytoplasm stained much deeper with eosin than that of the tumor cells. In many

places the tumor cells infiltrated the alveolar septums where they were intimately mixed with preexistent mesenchymatous cells. It seemed that the tumor cells sometimes contained coal pigment.

In the heart, the tumor formed a solid mass in the subepicardial layer, and strands of tumor cells had invaded the myocardium. Groups of muscle fibers were separated by tumor tissue, the tumor growing along the perivascular connective tissue; also single muscle fibers became thus isolated. Where the invading growth became very extensive, severe changes of the muscle fibers were found. They were transformed into a homogenous purple stained material. In the areas showing less intensive destructive changes, the muscle fiber often contained fine fat granules.

Fig. 3.—The pancreas replaced by tumor cells, the Islands of Langerhans and the pancreatic ducts having a marked resistance to invasion; ×70.

In the thyroid, in the center of the left lobe, a few vesicles were still intact. They were lined by a flat epithelium and contained a hemogenous acidophilic colloid. These vesicles were surrounded by others which were more or less severely changed. They were compressed by the growth of the tumor cells in the stroma; they were often empty or contained little colloid besides the desquamated and swollen cells. Their linings were sometimes cylindrical and glandlike. Other vesicles were very small and could hardly be distinguished from the stroma so rich in cells. In some places the vesicles were filled with larger round or oval cells which by the peculiar structure of their nuclei could be recognized as tumor cells. These areas resembled very much an alveolar carcinoma.

Large areas of the pancreas were replaced by tumor tissue, and in many places only the ducts and the islands remained. Here and there a small group of acinar tissue was found and one could follow the progress of the glandular cells as under the influence of the invading tumor cells they melted away. The greater resistance of the islands was striking, and often they were well preserved although embedded in tumor. There was an aberrent spleen in the tail of the pancreas, and the capsule of this splenic tissue resisted the invasion of the tumor, thus leaving the spleen free from it.

The suprarenal was surrounded by a solid tumor mass with which fat cells, blood vessels and nerve fibers were embedded. The blood vessels and nerves seemed to be well preserved. In some places the tumor broke through the capsule of the suprarenal and invaded parts of the cortex and the medulla. Cortical cells surrounded by tumor masses, lost their lipoid content, mingled with the tumor cells, shrunk and disappeared.

The histologic examination of the kidneys, lymph glands and liver revealed nothing to characterize further the nature of this tumor.

Anatomic Diagnosis.—Primary reticulum cell lymphosarcoma of the anterior mediastinum with metastasis to the lungs, heart, thyroid gland, cervical lymph glands, pancreas, liver, kidneys and suprarenals.

COMMENT

The difficulties which arise in the interpretation of the histogenesis of the normal thymus and the determination of the exact origin of the tumors of the anterior mediastinum are similar. The opinion of the majority of the histologists and embryologists seems to be that the thymus is purely an epithelial organ (Gottesman and Jaffé [1]), and a true thymic tumor may be expected to be one epithelial in structure (Brannon,[2] Foote [3]). The mesenchymatous tumors in this region of more or less lymphatic structure are apparently lymphosarcoma and appear to be derived from the lymph glands of the anterior mediastinum (Ghon and Roman,[4] Liegois and Foulon,[5] Foote and Friedlander [6]).

In the present case, epithelial structures were not found in the primary tumor or in any of its metastases. The tumor cells formed minute alveoli in places, but the cells were reticulated and their cytoplasmic branches fused with the fibrillar connective tissue (figs. 1 and 2).

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The macroscopic appearance of the tumor was white, elastic, homogenous, grew along the lymphatics and had a distinct tendency to infiltrative growth. There was a marked fibrosis of the primary growth with almost a complete absence of regressive changes, such as hemorrhage, fatty degeneration and necrosis. The final diagnosis of a reticulum cell (very immature) lymphosarcoma was made.

Of clinical interest was, first, the extensive involvement of the thyroid gland; because of the peculiar arrangement of the tumor cells in the microscopic section of the biopsy specimen, a primary carcinoma of the thyroid gland had to be considered; second, the metastases to the pancreas completely replacing this organ (fig. 3).

The relation between the mediastinum and pancreatic region was recently again observed in a case of a primary medullary carcinoma of the pancreas with large metastases to the mediastinum causing pressure necrosis and ulceration of the esophagus so that the clinical diagnosis of a primary carcinoma of the esophagus was made. The general distribution of the metastases to the other viscera was almost identical with the tumor described above.

SUMMARY

A case of a primary malignant tumor of the thymic region in a man, aged 35, is described. The tumor is classified as a reticulum cell lymphosarcoma, and its origin is traced to the lymph glands of the anterior mediastinum.

The interesting features of this case are especially: (*a*) the extensive metastases to the thyroid gland occasioning the preliminary clinical diagnosis of a malignant tumor of the thyroid; (*b*) extensive metastatic involvement of the pancreas without any invasion of the Islands of Langerhans. There was an aberrant spleen in the tail of the pancreas which resisted tumor invasion. There was no diabetes mellitus.

The suggestion is made to avoid the term "thymoma," since most of the tumors in this region are really lymphosarcoma. The only real thymic tumor is a carcinoma.

CONTROL OF COMPENSATORY HYPERPLASIA OF THE THYROID OF GUINEA-PIGS BY THE ADMINISTRATION OF IODINE *

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The thyroid gland is a very labile tissue, capable of marked and rapid compensatory hyperplasia in response to functional demands for increased activity. Experimentally the simplest means of producing compensatory hyperplasia is by partial removal, as first carried out by Wagner [1] and Halsted,[2] and in recent years by many other workers, on most of the available laboratory animals including sheep, goats, dogs, cats, guinea-pigs, rabbits, rats and mice.

If one removes from one half to three fourths of the thyroid gland from these animals, the remaining portion usually undergoes some degree of compensatory hyperplasia. The extent of the hyperplasia thus produced is known to vary with the species of animal, the diet, available iodine, the age of the animal, the season of the year and probably with other factors still unknown, in addition to the amount of thyroid removed.

In 1909, Marine and Lenhart [3] showed that this compensatory hyperplasia could be prevented in dogs by the administration of iodine even after as much as three fourths of the gland had been removed; that if much more than this amount was removed, iodine would not protect, although protection could be obtained with desiccated thyroid after the removal of five sixths of the gland. Since these observations were made, I have performed many similar experiments on cats and rabbits with the same results.

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* From the Laboratory Division, Montefiore Hospital.

1. Wagner, J.: Ueber die Folgen der Extirpation der Schilddrüse nach Versuchen an Thieren, Wien. med. Bl. **7**:771, 1884.

2. Halsted, W. S.: An Experimental Study of the Thyroid Gland of Dogs with Especial Consideration of Hypertrophy of This Gland, Johns Hopkins Hosp. Rep. **1**:373, 1896.

3. Marine, D., and Lenhart, C. H.: Effects of the Administration or the Withholding of Iodin-Containing Compounds in Normal Colloid or Actively Hyperplastic (Parenchymatous) Thyroids of Dogs: Some Experiments on (Congenital) Prenatal Thyroid Hyperplasia in Dogs; Remarks on the Clinical Manifestations Associated with Marked Thyroid Hyperplasia, Arch. Int. Med. **4**:253, 1909; Colloid Glands (Goiters): Their Etiology and Physiological Significance, Bull. Johns Hopkins Hosp. **20**:131, 1909.

In 1915, Manley and Marine [4] showed that iodine in very small doses caused involution of actively hyperplastic thyroid transplants in the abdominal wall of rabbits and also that when iodine was administered following transplantation no hyperplasia of the thyroid transplant ordinarily occurred during the time in which iodine was administered, provided a sufficient amount of the original thyroid gland (approximately one fourth) remained intact.

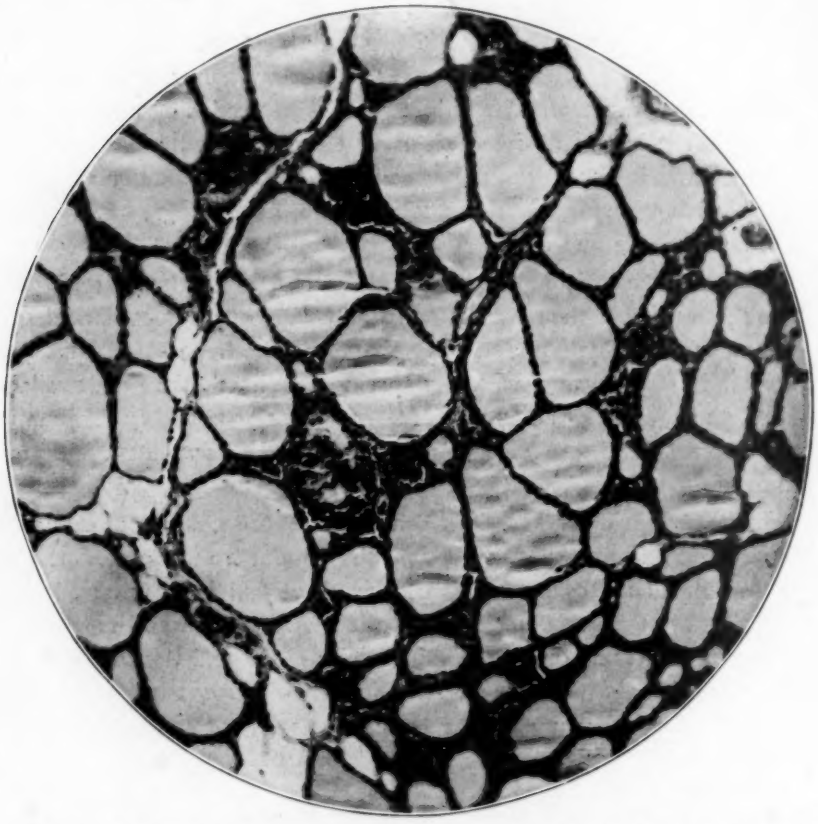

Fig. 1 (Guinea-pig 1-17 Control Specimen).—Follicular epithelium flat cuboidal, alveoli irregular medium sized and colloid uniform and normal.

In 1920, Loeb [5] reported experiments on guinea-pigs in which the administration of potassium iodide did not protect the remaining thyroid

4. Manley, O. T., and Marine, D.: Studies in Thyroid Transplantation. I. Data Relative to the Problem of Secretory Nerves, Proc. Soc. Exper. Biol. & Med. **12**:202, 1914-1915.

5. Loeb, L.: Studies on Compensatory Hypertrophy of the Thyroid Gland. IV. The Influence of Iodine on Hypertrophy of the Thyroid Gland, J. M. Res. **41**:481, 1919-1920.

against compensatory hyperplasia following the removal of the greater part of the gland. In 1926, Loeb[6] published a further study of the influence of the administration of potassium iodide on the remaining thyroid stump following "the removal of the greater part of the gland." In seventy-two guinea-pigs, potassium iodide was given sometimes subcutaneously and sometimes orally, in amounts varying between 0.1 and

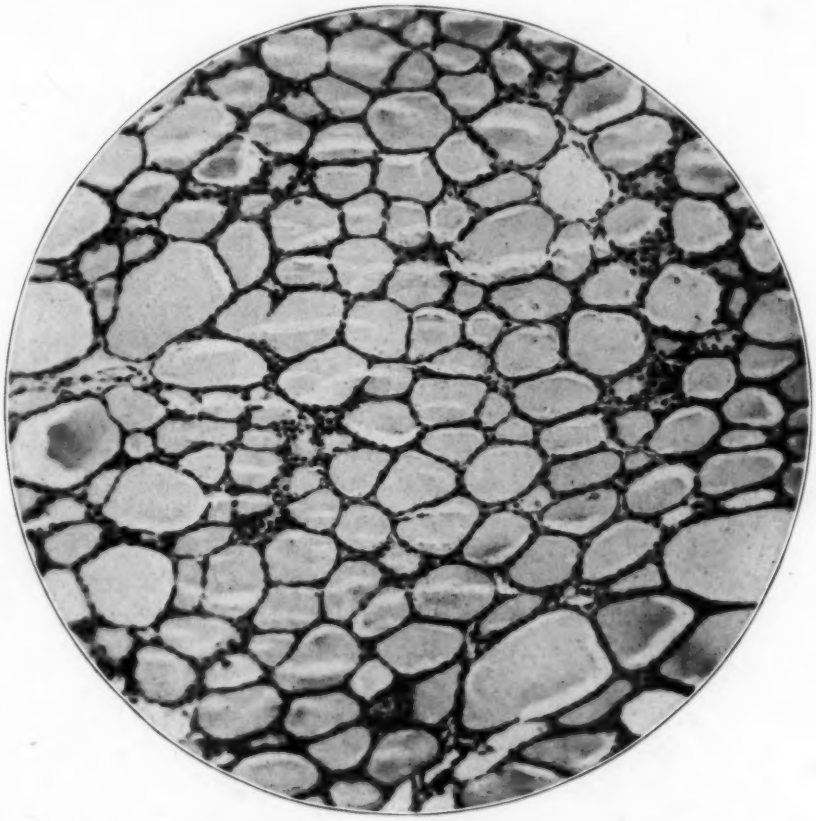

Fig. 2 (Guinea-pig 1-17 Necropsy Specimen).—Follicular epithelium flat, alveoli regular small, colloid dense (225 mg. of potassium iodide administered).

0.025 Gm. daily and over periods varying from seventeen to sixty-four days. His conclusions from these experiments were as follows:

On the basis of a very large number of experiments it could be definitely stated that potassium iodide does not prevent or even diminish the hyperplasia of the thyroid gland in the guinea-pig which follows extirpation of a great part of the

6. Loeb, L.: Studies on Compensatory Hypertrophy of the Thyroid Gland. VII. Further Investigation of the Influence of Iodin on Hypertrophy of the Thyroid Gland with an Interpretation of the Differences in the Effects of Iodin on the Thyroid Gland Under Various Pathologic Conditions, Am. J. Path. **2**:19, 1926.

thyroid gland. On the contrary in all our series of experiments the average of hypertrophy was greater in the animals which received potassium iodide than in the control animals.

His conclusions were so definite and yet so different from what usually has been obtained with the dog, cat and rabbit that we were led to repeat these experiments. It would be of greatest biologic interest if

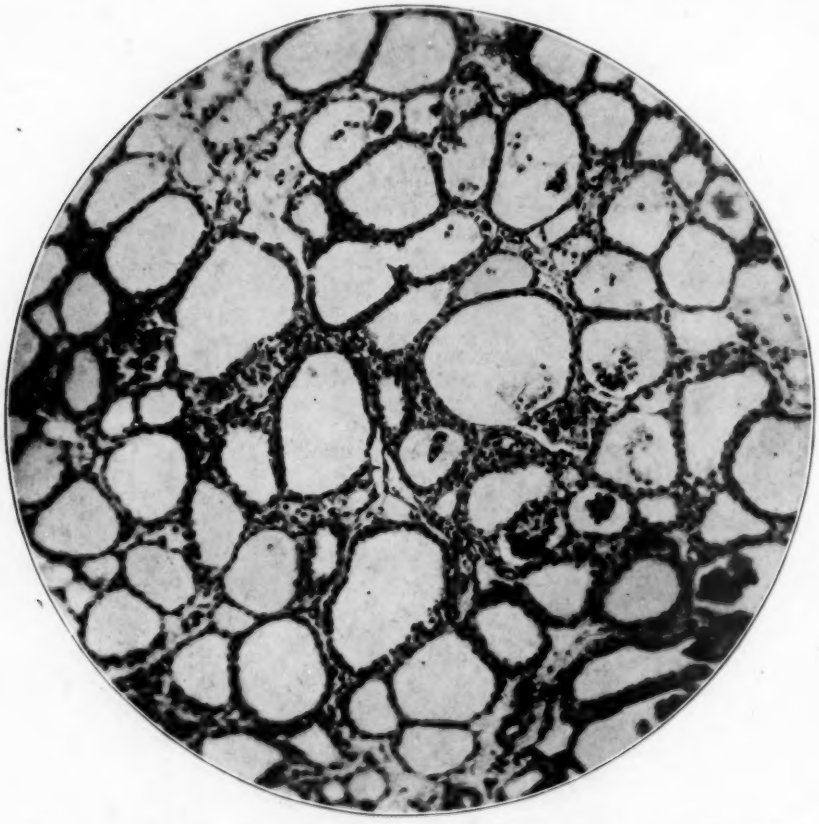

Fig. 3 (Guinea-pig 1-7 Control Specimen).—Follicular epithelium, low cuboidal, alveoli slightly irregular large, colloid possibly reduced.

the guinea-pig thyroid could be shown to behave differently in respect to compensatory hyperplasia from the thyroid of other mammals, especially since in its morphology, capacity to store iodine following its administration, and indeed in its reaction to desiccated thyroid (Loeb [5]), it behaves similarly to the thyroid of other mammals. The suspicion was aroused that perhaps Loeb's results could be explained on the basis of slight quantitative differences due to species and to the amount of thyroid removed (since even in dogs and rabbits iodine will not protect against compensatory hypertrophy if much more than three fourths of

the thyroid is removed) rather than that the thyroid of the guinea-pig was biologically different from that of other mammals.

The following experiments were carried out on sixteen guinea-pigs. All operations were performed under ether anesthesia with strict aseptic technic and, as in all our experiments in which the thyroid is involved, without the use of tincture of iodine for skin sterilization which is not kept on the floor where the animals are quartered.

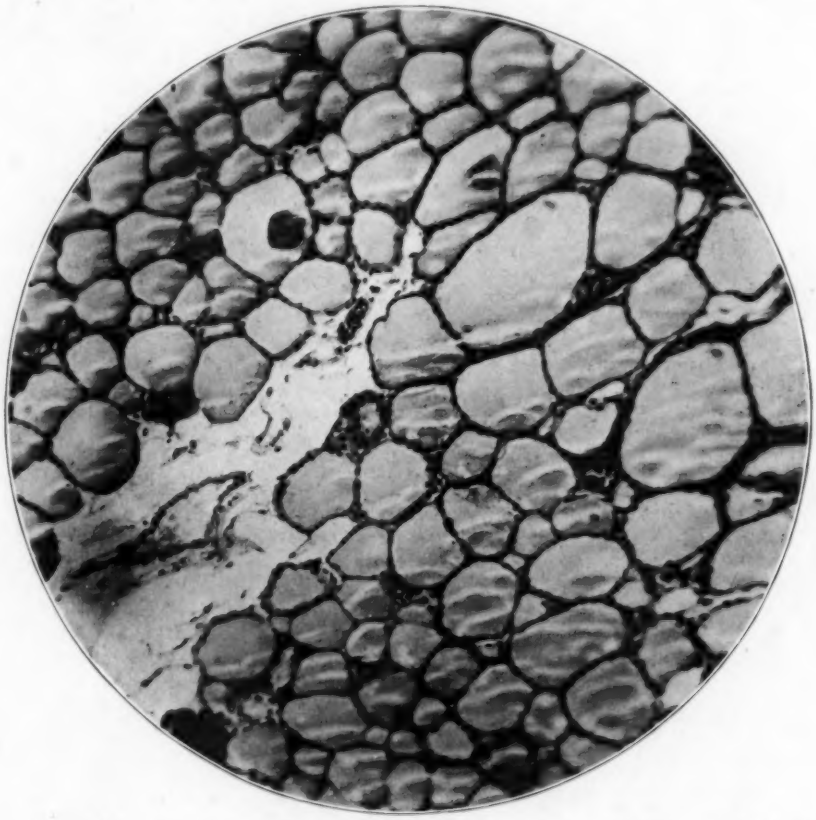

Fig. 4 (Guinea-pig 1-7 Necropsy Specimen).—Follicular epithelium flat, alveoli slightly irregular medium sized, colloid dense (175 mg. of potassium iodide administered).

On eight guinea-pigs, one entire lobe only was removed. Iodine in the form of potassium iodide was injected intraperitoneally in 25 mg. doses twice weekly in four animals, and the remaining four served as controls. On eight additional guinea-pigs, one entire lobe and approximately one half of the other lobe were removed (this was accomplished by exposing the lobe, passing a fine silk ligature around it, and, after adjusting it to as near the middle of the lobe as possible, tying it tightly

and cutting away the lower portion of the lobe with fine scissors). Into four of these guinea-pigs 25 mg. of potassium iodide in 1 cc. of water was injected intraperitoneally twice weekly while the remaining four served as controls. One animal died of pneumonia on the thirtieth day, while all the others remained healthy and gained in weight until killed between the thirty-third and thirty-ninth day following the partial thyroidectomy. The complete data of these experiments, including sex,

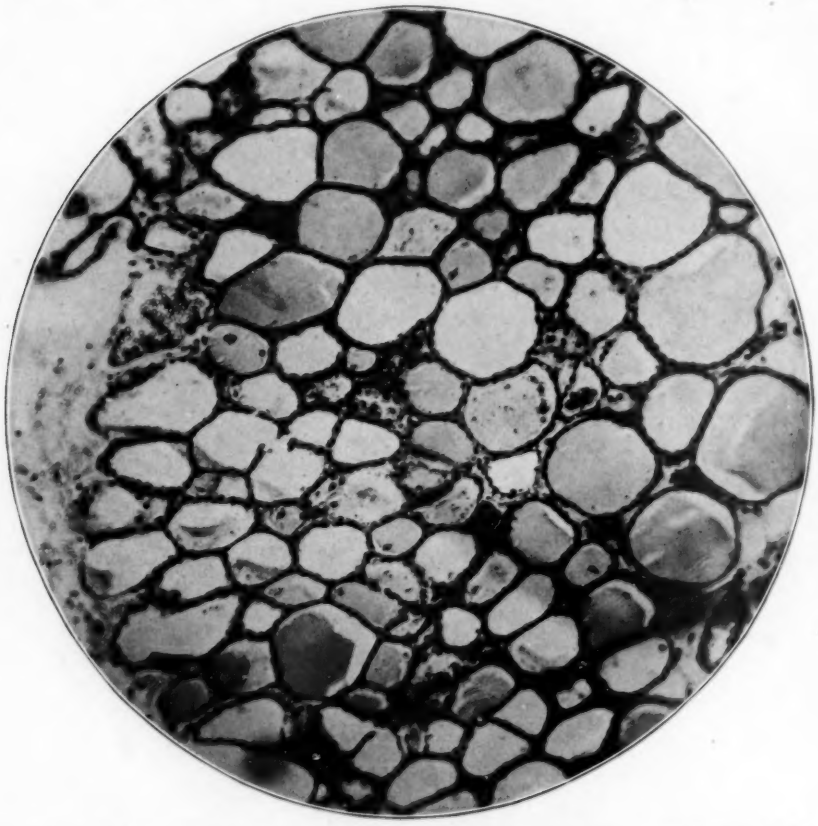

Fig. 5 (Guinea-pig 1-19 Control Specimen).—Follicular epithelium flat cuboidal, alveoli regular small, colloid uniform possibly reduced; operative congestion.

weight, duration of life, amount of thyroid removed, amount of potassium iodide given, and the gross and microscopic appearance of the thyroid removed at operation and at necropsy, are given in the table.

A description of the most important features of these experiments follows:

The gross appearance of the thyroid tissue removed at operation was strikingly similar. All glands were pale amber and translucent owing to abundant colloid. Microscopically (formalin fixation and hematoxylin

TABLE 1

No. of Guinea-Pig	Sex	Weight of Pig when Thyroidectomized, Gm.	Weight of Pig when Killed, Gm.	Interval in Days	Approximate Amount of Thyroid Removed	Amount of Potassium Iodide Given, Mg.	Gross Appearance of Thyroid at Operation	Amount and Gross Appearance of Thyroid Tissue at Necropsy	Microscopic	
									Removed at Operation	Removed at Necropsy
5	F	535	636	39	Right lobe	None	Pale, amber, translucent	Left—red, translucent, 11 × 4 mm. Right—none	Epithelium—low cuboidal Colloid—uniform	Cuboidal Possibly reduced (thyroiditis)
15	M	695	653	33	Left lobe	None	Pale, amber, translucent	Right—large, bright red Left—2 possible fragments	Epithelium—flat cuboidal Colloid—uniform	Flat cuboidal Reduced
16	M	519	632	38	Right lobe	None	Pale, amber, translucent	Right—possible fragment in suture Left—much enlarged (dark red with isthmus)	Epithelium—flat Colloid—dense	Flat cuboidal Normal
19	F	825	885	37	Right lobe	None	Pale, amber, translucent	Right—possible tiny fragment Left—very large, dark red	Epithelium—flat cuboidal Colloid—uniform	Low cuboidal Possibly reduced
7	F	522	605	33	Right lobe	175	Pale, amber, translucent	Right—none Left—very small, pale amber	Epithelium—low cuboidal Colloid—possibly reduced	Flat Dense, uniform
18	F	689	801	39	Left lobe	225	Pale, amber, translucent	Right—small, pale amber Left—none	Epithelium—low cuboidal Colloid—possibly reduced	Flat Dense
14	M	445	601	38	Right lobe	225	Pale, amber, translucent	Right—none Left—slightly enlarged pink, translucent	Epithelium—cuboidal Colloid—reduced	Flat Dense
11	M	821	826	37	Right lobe	225	Pale, amber, translucent	Right—none Left—vascular, not enlarged	Epithelium—flat cuboidal Colloid—slightly irregular; area with lymph foci and eosinophilic cells surrounding it	Flat Dense
4	F	578	708	38	Right lobe and ½ left	None	Pale, amber, translucent	Right—none Left—4 mm., pink, translucent, no definite regeneration	Epithelium—low cuboidal Colloid—uniform	High cuboidal Reduced
6	F	493	563	D.30	Right lobe and ½ left	None	Pale, amber, translucent	Right—none Left—bright red mass	Epithelium—low cuboidal Colloid—reduced, pale	Cuboidal reduced Reduced
10	M	625	747	39	Right lobe and ½ left	None	Pale, amber, translucent	Right—possibly tiny fragment Left—lobe sized, bright red, 12 mm. in length	Epithelium—low cuboidal Colloid—decreased, several distinct areas in which groups of alveoli have columnar epithelium with infoldings	Low cuboidal Reduced
13	M	721	768	37	Right lobe and ½ left	None	Pale, amber, translucent	Right—possible fragment Left—pink, translucent 5 × 5 mm. and possible fragment	Epithelium—flat cuboidal Colloid—possibly reduced	Flat cuboidal Dense
8	F	668	768	38	Right lobe and ½ left	225	Pale, amber, translucent	Right—none Left—pink, translucent, 4 × 5 mm.	Epithelium—low cuboidal Colloid—normal, possibly reduced	Flat Dense
9	M	492	622	39	Right lobe and ½ left	225	Pale, amber, translucent	Right—none Left—very pale, translucent, 4 × 5 mm.	Epithelium—flat cuboidal Colloid—possibly somewhat reduced	Flat Dense
12	M	620	745	33	Right lobe and ½ left	200	Pale, amber, translucent	Right—possible fragment Left—pinkish, translucent, 3 × 3 mm.	Epithelium—low cuboidal Colloid—slightly reduced	Flat Dense
17	F	831	868	37	Right lobe and ½ left	225	Pale, amber, translucent	Right—possible fragment Left—pink, translucent, 4 × 4 mm.	Epithelium—flat cuboidal Colloid—uniform and normal	Flat Dense

and eosin stain), the colloid was uniform and abundant. The follicular epithelium varied only within narrow limits, being flat in one instance, flat cuboidal in six, low cuboidal in eight and cuboidal in one. The gross appearance of the thyroid found at necropsy was strikingly more red and vascular in those that did not receive iodine, and the remaining thyroid of those from which approximately one and one-half lobes were removed was more vascular than was that in those animals from which

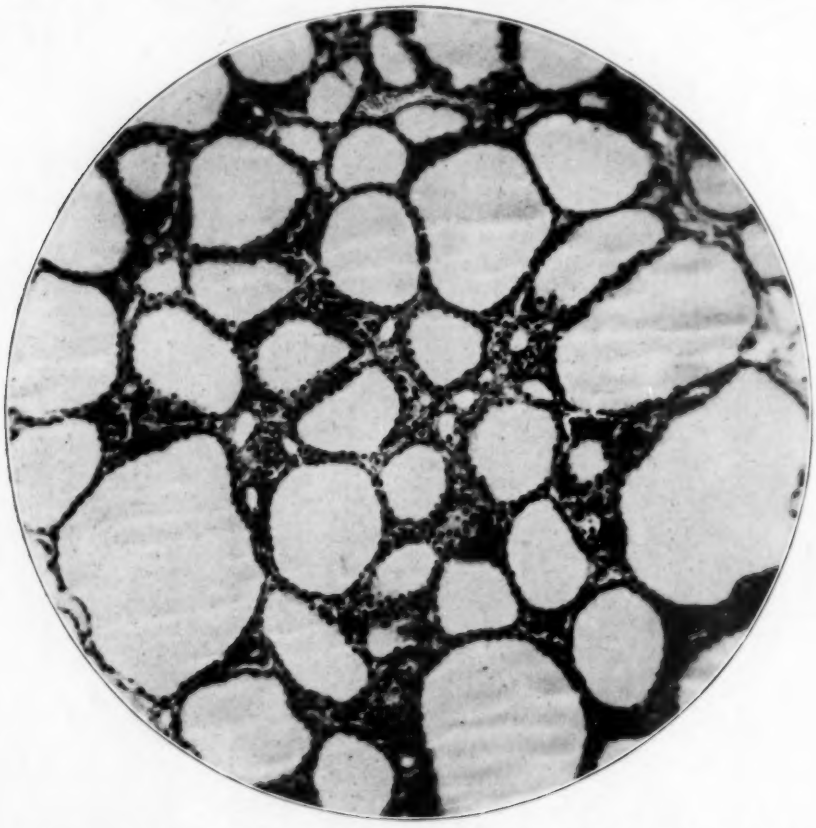

Fig. 6 (Guinea-pig 1-19 Necropsy Specimen).—Follicular epithelium low cuboidal, nuclei enlarged and vesicular follicles irregular in size, colloid uniform and reduced.

only one lobe had been removed. It was therefore possible to distinguish grossly those thyroids which had received iodine from those which had not by the difference in colloid (vascularity).

Microscopically the follicular epithelium in the four animals from which one lobe only was removed and no iodine administered was found to be cuboidal in one, low cuboidal in one and flat cuboidal in two. In the four animals in which one lobe only was removed and potassium

iodide was administered the follicular epithelium was flat in all. The colloid stained much more densely in those receiving iodine, although it was present and uniformly distributed in the follicles of the control thyroids.

Of the four animals from which one and one-half lobes were removed and potassium iodide given, the follicular epithelium was flat in each instance, and definitely lower than in the portion of the thyroid removed

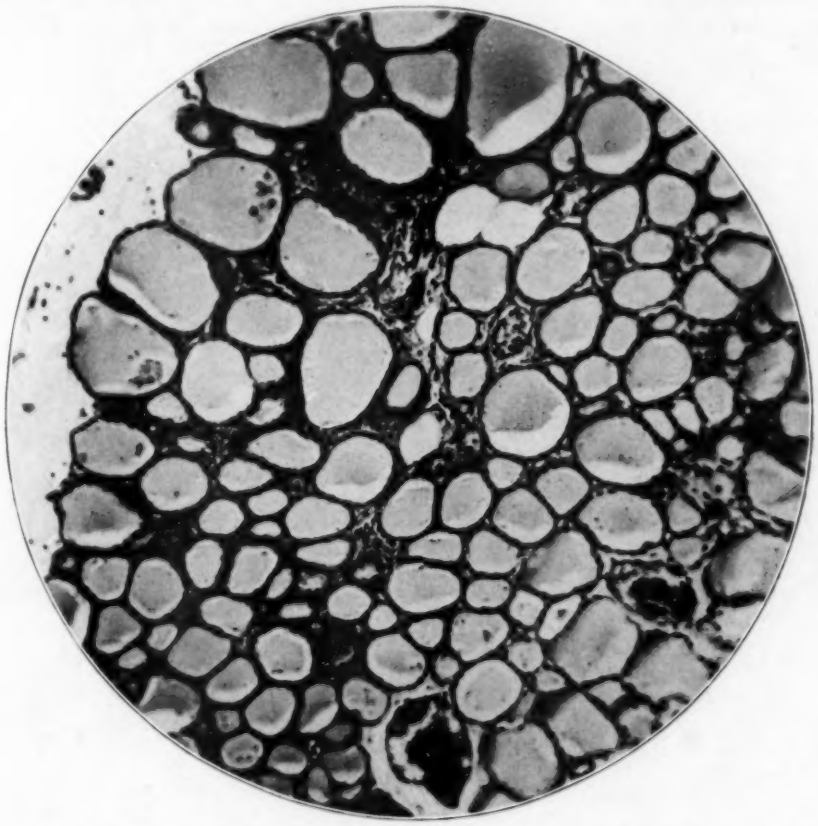

Fig. 7 (Guinea-pig 1-4 Control Specimen).—Follicular epithelium low cuboidal, follicles small, colloid uniform normal.

at operation. This observation clearly demonstrated that iodine not only exerted an inhibitory action on compensatory hyperplasia, but actually involuted the follicular epithelium of the remaining thyroid stump after the removal of one and one-half lobes. Of the four guinea-pigs from which approximately one and one-half lobes were removed and no iodine administered, the follicular epithelium changed from low cuboidal to high cuboidal in one (guinea-pig 4), from low cuboidal to cuboidal in one (guinea-pig 6) and remained unchanged in two.

COMMENT

Suspecting that Loeb had removed too much of the thyroid and thus masked the protective effect of iodine, we purposely removed only one and one-half lobes as a maximum and one lobe as a minimum. The resulting compensatory hyperplasia was accordingly slight but definite, and the inhibiting effect of iodine was absolute and clear cut. It is obvious from these results that iodine would have protected against

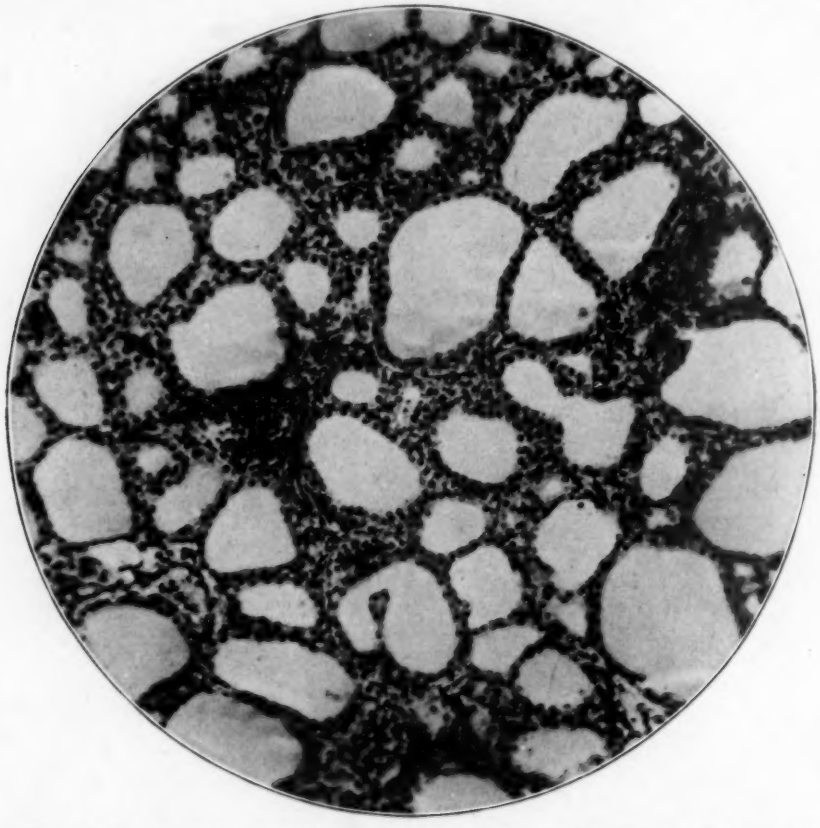

Fig. 8 (Guinea-pig 1-4 Necropsy Specimen).—Follicular epithelium high cuboidal, nuclei very large, pale, vesicular, beginning infoldings and definite budding, follicles irregular, colloid reduced.

compensatory hyperplasia even after removal of more that three fourths of the gland, but we were concerned only with determining whether or not iodine exercises a protective influence against compensatory hyperplasia, and the experiments were planned only with this point in view. From a more extensive experience with similar experiments in the dog, cat and rabbit, we could predict that iodine will protect the guinea-pig thyroid just as it does the rabbit thyroid against compensatory hyper-

plasia after removal of a greater amount of the gland than is the case with dogs and cats. The underlying cause of the thyroid hyperplasia occurring in goiter development might be different from the hyperplasia caused by partial removal of the thyroid, but the difference could not be demonstrated by any difference in their behavior toward iodine, which in our experience is identical. Iodine will prevent both, and it will involute both the compensatory overgrowth of simple goiter and that following partial removal. The guinea-pig is not a favorable animal for thyroid work. The gland is difficult to expose for operative procedures, and regeneration takes the form of new follicle formation by budding while the epithelium is still cuboidal (Seecof). In the cat and dog, on the other hand, a marked hypertrophy of the follicular epithelium going on to high columnar epithelium with infoldings and plications occurs before new follicle formation begins. This difference provides a delicate morphologic means of estimating the milder degree of compensatory hypertrophy in the dog and cat which is not available for the guinea-pig. Iodine determinations are an even more delicate means of measuring compensatory hypertrophy than morphology when sufficient tissue is available for analysis, but it is more difficult, and when working with such small amounts of tissue as are available in guinea-pigs, the errors are too great for use.

SUMMARY

One thyroid lobe was removed from each of eight guinea-pigs and approximately one and one-half lobes from each of eight additional guinea-pigs. Twenty-five milligrams of potassium iodide in 1 cc. of water was injected intraperitoneally twice weekly over approximately four and one-half weeks in four guinea-pigs of each group. This amount of iodine completely protected against compensatory hyperplasia of the remaining thyroid in both groups, while the control guinea-pigs showed in most instances slight but definite compensatory hyperplasia. It is certain from these experiments, however, that iodine will not only protect against compensatory hyperplasia of the thyroid in guinea-pigs as in other animals, but will also cause involution of any existing hyperplasia even after the removal of three fourths of the gland. Compensatory hyperplasia of the thyroid is not so readily produced in guinea-pigs as in carnivorous animals, although the basic biologic reactions are the same, and it is probable that age, diet, season and general nutrition will exert an influence on the guinea-pig thyroid similar to that noted in other animals.

It is suggested that Loeb's failure to obtain protection against compensatory hyperplasia of the thyroid of guinea-pigs by the use of iodine was due to the removal of too much thyroid.

TWO CASES OF CHIARI'S NETWORK*

WILLIAM R. JORDAN

UNIVERSITY, VA.

A certain cardiac anomaly was first reported in 1897 by Chiari [1] and for this reason is called "Chiari's network." The malformation, as described by Chiari, consists of a network of fibers in the cavity of the right atrium, varying from fine threads to rather coarse bands, 2 mm. in width. There may be a dense, spreading network or merely a large band with a few finer filaments. The attachments of these fibers vary somewhat, but in general they extend from the vicinity of the interatrial septum and crista terminalis to the tips of the thebesian and eustachian valves or the tissue in that region. Thus, the network is in rather close relationship to the openings of the coronary sinus and the venae cavae.

From a study of the embryonic development of the heart, Chiari reached the conclusion that the "network" represents a flaw in development, and that the threads are "residues of the valvula venosa dextra and of the septum spurium."

In the embryonic development of the heart the single atrial cavity is divided into its two definitive chambers in the following manner: The septum primum arises from the middorsal wall of the atrium and eventually fuses with the endocardial cushions at the junction of the atrial and ventricular cavities. Perforation of the septum primum occurs to form the foramen ovale. This is subsequently closed by the fusion of the left valve of the sinus venosus and the septum secundum which appears in close proximity to the septum primum as an outgrowth from the ventral and caudal wall of the right atrium. The right horn of the sinus venosus lags somewhat and is taken up into the wall of the right atrium, which causes the opening into the right atrium of the superior and inferior venae cavae. The right valve of the sinus venosus at one time nearly divides the right atrium into two chambers; but later it becomes progressively lower, its cephalic portion remaining as the crista terminalis, its caudal portion being divided to form the valve of the inferior vena cava (eustachian valve) and the valve of the coronary sinus (thebesian valve). The septum spurium, later referred to, is merely a fusion of the right and left valves of the sinus venosus on the dorsal and cephalic wall of the right atrium.

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* From the Pathological Laboratory, University of Virginia.

1. Chiari, H.: Net Formation in the Right Atrium of the Heart (several drawings), Beitr. z. Path. Anat. u. z. allg. Pathol. **21**:1-10, 1897.

Since Chiari's report two other cases have been described. Lesieur and Froment [2] described a heart with a gaping foramen ovale and an anomalous valve of Thebesius 6 cm. high which stretched across the right atrial cavity. They attributed this to the maldevelopment of the left venous valve which failed to fuse with the septum secundum to close the foramen ovale. A less severe form of the condition was reported by Ebbinghaus.[3] In this case a fenestrated network extended from the eustachian valve across the cavity of the right atrium, and this was associated with fifteen small and two large perforations of the interatrial septum.

The hearts about which this report is made were obtained at necropsy.

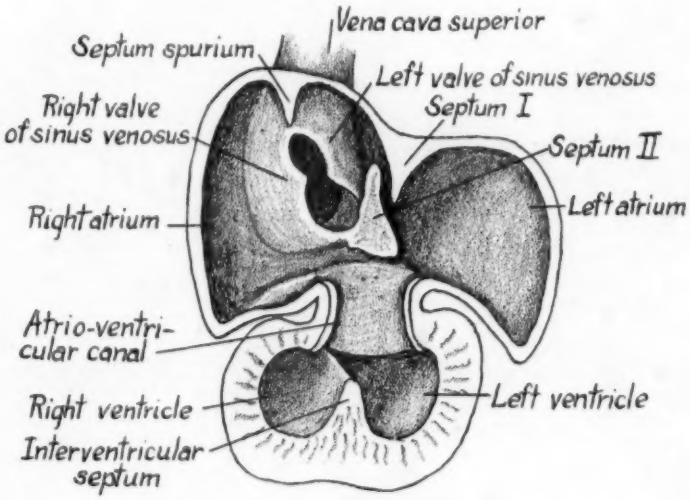

Fig. 1.—Inner view of dorsal wall of heart of 10 mm. human embryo. Drawn from a Ziegler model of one of His' embryos (Jordan and Kindred: Textbook of Embryology, New York, D. Appleton & Co., 1926).

NECROPSIES

A white man, aged 65, died of cancer and necropsy was performed. No lesions other than the bands were observed in the heart, but there were various other defects as follows: colloid carcinoma of the prostate, bladder and ribs; adenoma of the thyroid; multiple lipomas; polyp of hard palate; flat and pedunculated papillomas of the skin; and pigmented moles. The heart is shown in figure 2. The anomaly consisted of several filaments arising from the wall of the right atrium and joining successively to form a thicker central band which, in turn, gave off at intervals other filaments that were inserted in a manner similar

2. Lesieur and Froment: Lyon med. **96**:1045, 1911.

3. Ebbinghaus, mentioned by Abbott, Maude E.: Congenital Heart Disease, in Osler and McCrae; Modern Medicine, ed. 2, Philadelphia, Lea & Febiger, 1915, vol. 4, p. 353.

to the first. Three bands arose from the interatrial septum above the fossa ovale which in this case was deep. They converged as they descended in the atrial cavity and were joined by two bands from the crista terminalis. This relatively coarse band was joined by three more bands from the posterior atrial wall just cephalad to the opening of the inferior vena cava. As the band extended caudally, it gave off successively five bands that were attached in a row on the floor of the atrium from the vicinity of the coronary sinus to the eustachian valve, which, however, was not involved. A sixth band extended downward to be inserted directly into the thebesian valve. All of these bands arose from the endocardium by a broad thin base which gradually became rounded to form a band. The network, as such, was not taut, but, on the contrary, was very lax.

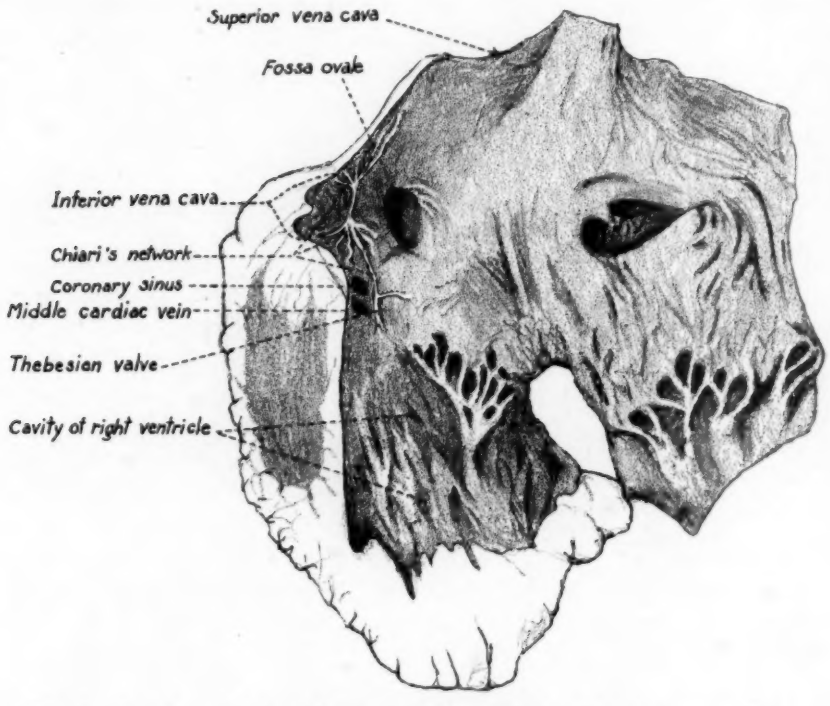

Fig. 2.—Interior of right atrium and right ventricle of heart from case 1.

A man, aged 71, died of uremia following kidney disease and necropsy was performed. No malformations other than the one in question were observed in the heart. One broad, coarse band arose from the posterior atrial wall just medial (toward the septum) and caudal to the opening of the inferior vena cava. This then split into three filaments, one of which attached directly to the thebesian valve and the other two in the near vicinity of, yet slightly lateral to, the opening of the coronary sinus.

Sections of the bands in each case showed that the coarser bands contained cardiac muscle which was surrounded by areolar connective tissue and that the whole was covered with endothelium continuous with that lining the heart. The fine bands were similar except that they contained no cardiac muscle. No elements of the bundle of His were observed in the bands.

As these bands arise from the interatrial septum in the region developed from the left valve of the sinus venosus and also from the crista terminalis which is the remains of the cephalic portion of the right valve of that sinus and as they insert in close proximity to and directly on the thebesian and eustachian valves, it seems that Chiari's explanation is proper. However, the left valve of the sinus venosus is also involved.

The occurrence of this anomaly is apparently more frequent than the literature indicates, and closer attention will probably reveal many such cases. A third case was noticed here about two years ago. The pathologic significance of the bands is not entirely clear. In the cases reported by Lesieur and Froment interference with the circulation and aeration of the blood occurred. In mild forms of the condition no circulatory disturbances have been reported, although the position of the bands with respect to the blood returning to the heart would seem to afford a favorable site for the formation of thrombi. Also the close relationship between the network and part of the conducting system would lead one to suspect that the network, or disease of the network, might occasionally influence the cardiac rhythm. It is a coincidence that at the time of death each of the men in the cases just described suffered from auricular fibrillation; but, in fact, each had sufficient cause for the fibrillation, quite aside from the "network."

AN UNUSUAL MALFORMATION OF THE RIGHT RENAL ARTERY*

MAX PINNER, M.D.
CHICAGO

A full term male infant died suddenly forty-eight hours after birth with symptoms of asphyxiation. Necropsy revealed as cause of death an extensive subdural hematoma covering fully the right half of the cerebrum. With the exception of the malformation to be reported here, no other significant pathologic condition was found.

The right renal artery in its peripheral half was dilated to an internal circumference of 2.2 cm. At the middle of the renal artery, beginning from its interior circumference, hung a sac which was in open connection with the lumen of the renal artery. It measured 9 cm. in length and 2.3 cm. in circumference. It ran parallel to the abdominal aorta and was loosely connected at its end with the connective tissue near the fundus of the urinary bladder. The wall of this sac had grossly the appearance of an artery; the sac contained some clotted blood; no opening could be found at the lower end of the sac, nor an internal spermatic artery.

The kidney showed a slight degree of fetal lobulation. After sectioning the organ in the usual way, the dilated renal artery was seen to end in a cavity which occupied the lower two thirds of the kidney and which had grossly a striking resemblance to a cardiac ventricle, showing ridges like trabecular muscles and being completely covered with what appeared to be true endothelium. There was a small pelvis in the upper pole with a ureter, leaving the organ anteriorly to the artery. The renal vein was very small and took its origin close to the ureter. Pelvis and cavity were separated by a thin bridge of renal tissue.

Sections through the wall of the vascular cavity in the lower pole, stained by Weigert's elastic method, showed a narrow zone of compressed renal tissue, a band of connective and thin, smooth muscle fibers, interspersed a few vasa vasorum, a slightly irregular external and internal elastic membrane, and between them irregular connective tissue and elastic fibers, and an endothelial layer. Neither macroscopically nor microscopically was it possible to find any vascular connections between the cavity and the renal tissue.

Sections through the wall of the arterial sac showed the structure of a medium sized artery in which the elastic fibers were slightly irregular in their course.

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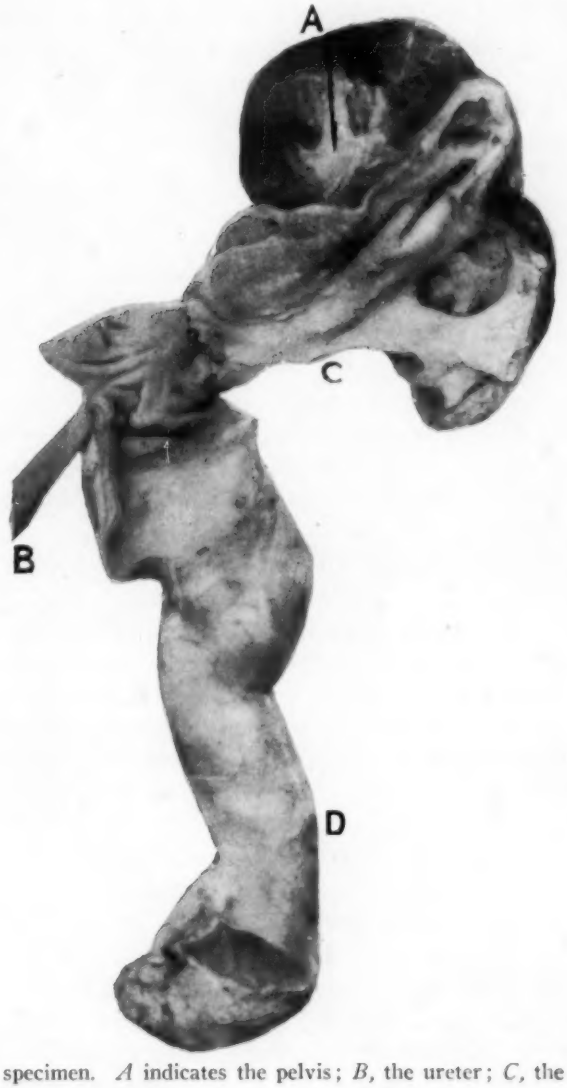
* From the Research Laboratories of the Municipal Tuberculosis Sanitarium.



Necropsy specimen. *A* indicates the pelvis; *B*, the ureter; *C*, the renal artery, and *D*, the aneurysmic sac.

COMMENT

I have not been able to find any reference in the literature to a similar malformation. The absence of a normal internal spermatic artery and the location of the arterial sac make it probable that this sac is a dilatation of the spermatic artery, although the sac ends blindly. No explanation is offered for the cause of this enormous dilatation nor for the formation of the vascular cavity in the kidney.

REVERSIBLE AND IRREVERSIBLE SWELLING OF LIVING AND OF DEAD CELLS*

BALDWIN LUCKE, M.D.

AND

MORTON McCUTCHEON, M.D.

PHILADELPHIA

One of the fundamental properties of animal cells is their ability to undergo increase in volume under certain conditions. Aside from such normal processes as growth and increased function, certain pathologic conditions lead to swelling of tissue cells. Cloudy swelling, hydropic degeneration, and coagulation necrosis are conditions of abnormal volume increase well known to pathologists. Among the factors capable of producing such changes, acutely acting toxic substances are believed to be important. The mechanism of the action of such substances remains obscure, in spite of numerous studies employing the usual histologic procedures of fixation and staining, as well as a smaller number of investigations on cells isolated from living animals.

From the experimental side, the most significant contributions to our knowledge of pathologic swelling of cells have been made by Hamburger [1] and Martin Fischer.[2] These workers reported that pieces of organs as well as isolated cells swell in certain acid solutions, and believed that in the mammalian body similar swelling occurs as the result of increased local acidity (for objections to this theory see Crozier,[3] Beutner,[4] and Henderson [5]).

Hamburger [1] and Fischer [2] did not show whether the cells or tissues were alive or dead at the end of their experiments. Yet this is a question of fundamental importance to the general pathologist. It would be of great interest to know whether cells which have undergone swelling as the result of injury are capable of returning to their normal state or whether they have been permanently damaged, perhaps even killed. Furthermore, it is important to determine whether substances other than acids may produce cellular swelling, and whether such swelling is reversible or irreversible.

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* From the Laboratory of Pathology, University of Pennsylvania School of Medicine, Philadelphia, and the Marine Biological Laboratory, Woods Hole.

1. Hamburger, H. J.: Osmotischer Druck und Ionenlehre, Wiesbaden, 1902-1904.

2. Fischer, M. H.: Ztschr. f. Chemie u. Industrie d. Kolloide **8**:159, 1911; Oedema und Nephritis, ed. 3, New York, 1921.

3. Crozier, W. I.: J. Am. Chem. Soc. **40**:1611, 1918.

4. Beutner, R.: Bio-chem. Ztschr. **39**:280, 1912.

5. Henderson, L. J., and Cohn, E. J.: J. Am. Chem. Soc. **40**:857 and 867, 1918.

The choice of material is of great importance in experiments on the effects of injury. The use of pieces of organs is open to several objections. If such pieces are weighed or measured in bulk, changes in the amount of intercellular fluid are a disturbing factor; the weight or dimensions of these preparations are not good criteria of cell volume. If individual cells are measured, such measurements are necessarily inaccurate on account of irregularities in the shape and size of the cells. Further, injury to the cells is likely to be inflicted in cutting up the tissues, the extent of such injury not being readily determinable.

For these reasons it is highly desirable to work with isolated cells, of regular shape (preferably spherical), which can be studied in their natural medium, and therefore without injury except such as is deliberately induced by experimental procedure. And it is important that cells should be chosen which can be made to give a definite criterion of viability.

In selecting such material, we are not limited in our choice to mammalian cells, since swelling appears to be a fundamental property of protoplasm. This assumption, if accepted, justifies us in following the methods of general physiology and selecting whatever type of cell seems most suitable for the experiment, and then applying the results tentatively to cells in general, being careful, however, to remember that such generalizations may need to be modified later for particular types of cells.

The unfertilized egg of the sea urchin, *Arbacia,* seems an almost ideal cell for the study of volume changes. Great numbers of isolated cells can be obtained readily and examined in their natural medium, sea water, in which they will remain alive for many hours. The cells are nucleated, have an abundance of cytoplasm, and behave as if they were surrounded by a semipermeable membrane. They are large, fairly uniform in size, as a rule perfectly spherical, and hence can be measured accurately. On conclusion of the experiment, it is a simple matter to determine whether the agents used have produced injury or death, for the addition of sperm will rapidly bring about cleavage in uninjured cells, while no division will take place in dead cells. Finally, gelation or coagulation of the protoplasm can be shown by the failure of the cell contents to separate into four distinct zones when subjected to brief centrifugalization.

In attacking a problem of such great complexity as the swelling of cells, it is clearly necessary to study one phase of the subject at a time. We have previously investigated the kinetics of osmotic swelling,[6] and the effect of hydrogen ion concentration on cellular swelling.[7] The present investigation is limited to the nature of swelling brought about in cells by various acutely acting injurious agents. We are not at the

6. McCutcheon and Lucke: J. Gen. Physiol. **9**:697, 1925-1926.
7. Lucke and McCutcheon: J. Gen. Physiol. **9**:709, 1925-1926.

present concerned with volume increase associated with increased function, growth, or with storage or nonassimilation of food material.

We shall now define more exactly the aim of the experiments which we are about to report. We sought first to determine what kinds of agents are capable of producing swelling of cells, and whether swelling produced by acids differs in any respect from that produced by other agencies. Second, we proposed to find under what conditions swelling is reversible, and under what conditions irreversible changes such as coagulation and death occur. Fortunately, we were able to obtain very clear-cut answers to these questions. It occurred invariably that when swelling was reversible, that is, when the cell returned to its normal size after having been restored to a normal environment, we were able to fertilize the eggs successfully, showing that no lasting injury had been produced; while invariably when the swelling was irreversible, it was associated with a permanent gelation or coagulation, and such eggs were incapable of fertilization and cleavage.

MATERIAL AND METHODS

The ovaries were removed from recently caught animals (avoiding contamination with body fluid and gut material), gently shaken in a bowl of sea water, and the eggs separated by straining through cheese cloth. After settling, the cells were washed twice with fresh sea water. Control samples were then measured and fertilized. All measurements were made with an ocular screw micrometer; the objective was immersed directly in the medium containing the cells; this system gave a magnification of 240 diameters. Since the eggs are spherical, their volume is directly proportional to the diameter, and hence can readily be calculated.

The effect of various agents was determined by dissolving them in sea water and adding a suspension of cells. At intervals a number were removed, washed, and returned to ordinary sea water, in which 10 or more were measured immediately as well as several hours afterward. In other series a few cells, usually from 3 to 5, were kept under continuous observation. At intervals or at the end of the experiment a freshly prepared suspension of sperm was added: in general, normal cleavage indicated absence of injury; atypical cleavage, injury; and failure to undergo cleavage, severe injury or death. In a number of experiments cells were subjected to centrifugalization under conditions which produce "zoning" of the cell contents into four distinct layers. Failure to "zone" represents change of consistency in the direction of gelation or coagulation. Since other eggs from the same experiment did not divide after addition of sperm, the gelation may be regarded as irreversible and indicating cell death.

The following agents were employed in attempts to produce swelling of cells: hypotonic sea water, hydrochloric acid, salicylic acid, carbon dioxide, sodium hydroxide, ammonium hydroxide, ether, heat, physiologically unbalanced solutions, amino acids, atropine and bacterial toxins.

Unless otherwise stated, the temperature of the solutions was from 23 to 24 C.

RESULTS

The results summarized below were based in each case on a minimum of three separate experiments.

Effect of Hypotonic Solutions.—The *Arbacia* egg is ordinarily in osmotic equilibrium with sea water. When it is placed in sea water diluted with distilled water, there occurs diffusion of water into the cell, which then swells. We found that this swelling began immediately and proceeded in such a regular way that when volumes were plotted against times very smooth curves were obtained. The volume of the cells at equilibrium was found to be inversely proportional to the osmotic pressure of the outside fluid. During these volume changes the cells preserved their spherical shape, unless cytolysis occurred. But unless

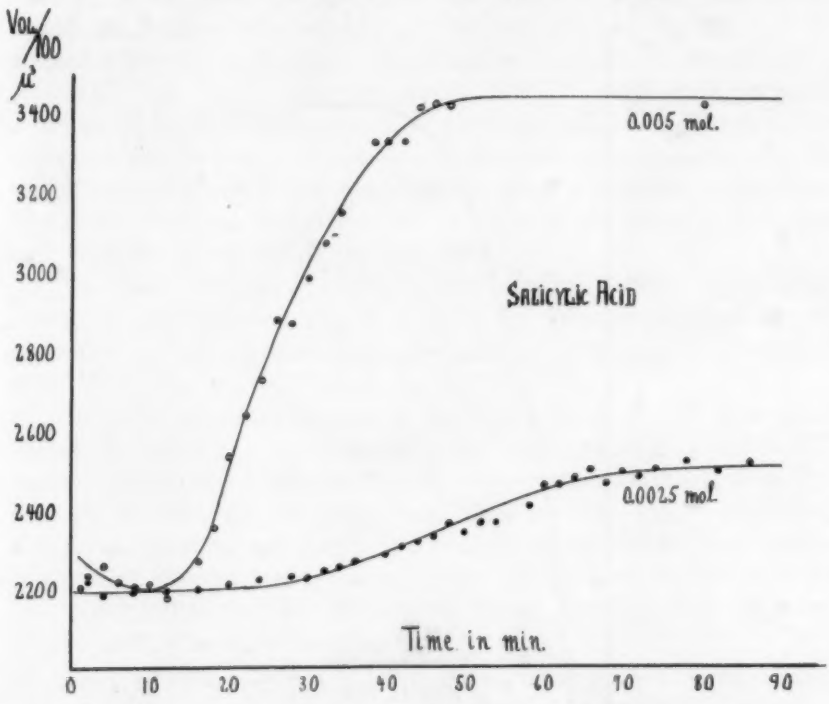

Chart 1.—A typical experiment on swelling of unfertilized Arbacia eggs in salicylic acid dissolved in sea water. Volumes $\times 10^{-2}$ are given in cubic microns and plotted against times. Each observational point represents the mean volume of 5 cells. The mean volume of control is 2207×10^2 cubic microns. The graph shows that the rate and the magnitude of swelling depend on the concentration of the injurious agent.

cytolysis occurred, the cells were in general uninjured by the experimental procedure, for when they were returned to ordinary sea water and sperm added, cleavage usually resulted. (The details of these experiments have been published elsewhere [6]).

We come now to the reversibility of the process. When eggs swollen in hypotonic sea water were replaced in ordinary sea water, they

returned to normal size. The following is a typical experiment: Eggs having a mean normal diameter of 73.5 ± 0.3 microns were placed in diluted sea water (sea water 80 parts, distilled water 20 parts). After twenty minutes their diameter had increased to 78.8 ± 0.2 microns. They were then transferred to ordinary sea water. Measurement at the end of one hour showed that they had returned to their former size (diameter 73.4 ± 0.2 microns). When more dilute sea water was used (sea water 60 parts, distilled water 40 parts) the diameter at the end

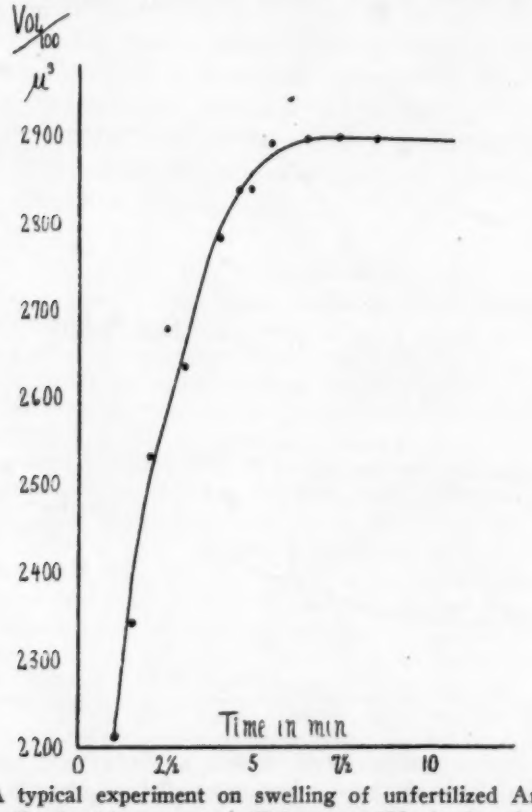

Chart 2.—A typical experiment on swelling of unfertilized Arbacia eggs in 5 per cent ether dissolved in sea water. Volumes × 10^{-2} are given in cubic microns and plotted against times. Mean volume of control is 2205 × 10^{3} cubic microns. The graph shows that the volume increase begins and ends abruptly.

of twenty minutes was 83.9 ± 0.2 microns, and after return to ordinary sea water, 74.6 ± 0.1 microns. By adding sperm, it was shown that the reversible swelling did not interfere with subsequent fertilization and cleavage.

In brief, then, change in the osmotic concentration of the medium brings about reversible swelling in living cells; within certain limits of length of exposure, concentration and temperature, no injury is produced.

Effect of Acids.—We have compared the effects of three acids possessing widely different properties: carbonic, hydrochloric and salicylic acids. Carbonic acid enters cells almost instantaneously and is relatively noninjurious. Hydrochloric acid enters very slowly and only when the cell has been severely injured or killed. Salicylic acid penetrates with great rapidity and is extremely toxic.

In the experiments with hydrochloric acid, it was found that volume change occurred only in the two most acid solutions used, at p_H 3 and 4, and in these only after long exposure. It was noted that the degree of swelling varied with the acidity of the solution An interesting and significant relation was brought out between volume changes and the ability of the egg to develop: loss of ability to divide preceded volume increase. The fact stands out clearly that no swelling occurred in solutions of hydrochloride acid until after the cells had suffered injury so severe that they were incapable of subsequent development. By the use of the centrifuge it was demonstrated that the cells were coagulated. The swelling proved irreversible, for on return to sea water no shrinkage took place in the course of several hours.[7]

The results obtained by exposing cells to carbon dioxide were similar, in that no swelling occurred as long as the cells remained uninjured. However, volume increase was inconspicuous even in injured or dead cells.[7]

The effect of salicylic acid is illustrated by a typical experiment shown in figure 1. The concentrations used were 0.005 and 0.0025 molar. In both concentrations the cells were coagulated in one minute or less, but swelling did not take place for some time after coagulation. The rate of swelling and the volume attained at equilibrium were greater in the more concentrated solution. After equilibrium was attained, the cells were transferred to ordinary sea water, in which they remained swollen until disintegration occurred.

Effect of Ether.—This substance was selected as a typical lipoid solvent, and used in concentrations of from 0.5 to 5 per cent. It is known that low concentrations diminish and high concentrations increase the viscosity of protoplasm (Heilbrunn [8]). We found that ether caused irreversible swelling in concentration of 3 per cent or over. The swelling was preceded or accompanied by irreversible coagulation. A typical experiment is represented in figure 2, in which it is shown that the swelling occurs very rapidly, and that equilibrium is reached in less than ten minutes. We made numerous attempts to demonstrate reversibility of the process by exposing the cells for very brief periods—ten seconds, twenty seconds and longer. But in no instance were we able to find that uninjured cells increased in volume, or that injured or dead cells which had swollen regained normal size when transferred to pure sea water.

8. Heilbrunn, L. V.: Biol. Bull. **49**:461, 1925.

Effect of Heat.—Cells were placed in sea water of different temperatures, constant to ± 1 degree. At stated intervals samples were removed and distributed into several large bowls of sea water at room temperature. One lot was measured immediately, and after measurement sperm was added; another lot was measured several hours afterward to determine possible changes in volume; a third lot was subjected to centrifugation.

The results of several typical experiments are shown in the table. It will be noted that the cells were not altered by exposure to a temperature of 30 C. from one to sixty-four minutes. At 35 C. there was no change in volume, but development was atypical after exposure for four minutes, and completely inhibited after thirty-two minutes; the cells failed to "zone" properly after four minutes, and were completely coagulated after

Effect of Temperature on Volume of Unfertilized Arbacia Eggs

Temperature C.	Control	Time of Exposure in Minutes				
		1	4	16	32	64
30	72.6 ± 0.2 C. Z.	73.8 ± 0.3 C. Z.	72.8 ± 0.4 C. Z.	72.0 ± 0.3 C. Z.	.....	72.4 ± 03 C. Z.
35	74.7 ± 0.2 C. Z.	74.4 ± 0.2 C. Z.	75.4 ± 0.3 A.C. S.Z.	74.6 ± 0.2 A.C. S.Z.	74.4 ± 0.2 N.C. N.Z.	
42	74.4 ± 0.2 C.	75.4 ± 0.2 A.C.	75.3 ± 0.3 N.C	75.2 ± 0.2 N.C.	76.9 ± 0.3 N.C.	75.3 ± 0.2 N.C.
52	73.9 ± 0.2 C. Z.	73.2 ± 0.2 N.C. N.Z.	76.4 ± 0.3 N.C. N.Z.	75.8 ± 0.4 N.C. N.Z.	76.4 ± 0.6 N.C. N.Z.	
60	74.5 ± 0.2 C. Z.	78.3 ± 0.7 N.C. N.Z.	.....	83.6 ± 0.9 N.C. N.Z.	84.8 ± 0.6 N.C. N.Z.	

Each figure represents the mean diameter in microns, plus or minus its probable error, of from 20 to 30 cells. After measurement, one lot of cells was returned to ordinary sea-water and sperm was added; C. indicates normal cleavage; A.C., atypical cleavage; N.C., no cleavage. Another lot was subjected to centrifugation; Z. indicates normal "zoning"; S.Z., slight "zoning," more viscous; N.Z., no "zoning," gelation.

thirty-two minutes. Exposure to 52 C. caused coagulation in all lots and a very slight volume increase. At 60 C. the cells coagulated immediately and increased in size in direct proportion to the length of exposure. The changes were irreversible in all lots.

Effect of Miscellaneous Agents.—Since the experiments with the other agents used brought out no facts different from those stated above, they may be summarized briefly.

Amino Acids.—Cells were exposed up to seven hours to solutions of the following amino acids: glutamic acid in saturated solution (less than 1 per cent), leucin 0.7 per cent, aspartic acid in saturated solution (less than 1 per cent), histamine 2 per cent, alanin 1 per cent, glycocoll 4 per cent. These substances were dissolved in sea water. The amino acids tested did not cause swelling. No development occurred after prolonged exposure to histamine, glutamic acid and aspartic acid.

Unbalanced Solutions.—Sodium chloride and sodium iodide were used in half molar concentration. Prolonged exposure produced irreversible swelling.

Alkalis.—Sodium hydroxide and ammonium hydroxide were dissolved in neutralized sea water to give a range of hydrogen ion concentration from 7.0 to 9.8. No definite swelling occurred.[7]

Bacterial Toxins.[9]—Tetanus, scarlet fever and diphtheria toxins were used in from 0.1 to 10 per cent concentration in sea water. The cells were exposed for several hours. These substances did not cause swelling.

Atropine.—Exposure to atropine sulphate in concentrations of twentieth, fortieth and eightieth molar for one and one-half hours did not cause volume change or produce coagulation; however, the cells developed atypically after the addition of sperm.

COMMENT

As the result of these experiments, it is possible to distinguish two types of cellular swelling. The first type occurred only when the osmotic pressure of the outside solution was lowered. Such swelling was reversible; for, provided that the cells were returned to ordinary sea water before cytolysis had occurred, they regained their normal size and function, and they were capable of fertilization and subsequent development. Therefore the cells had suffered no lasting injury.

The second type of swelling was induced by diverse injurious agents, such as acids, ether and heat. In contrast to the first type, this swelling was irreversible, for the cells never returned to normal size when the injurious agent was removed. These cells were killed, for they were coagulated and incapable of being fertilized. This kind of swelling is therefore associated with cell death.

It is evident that in both cases volume increase was due to absorption of water. In the case of reversible swelling (in hypotonic solutions), absorption of water is produced by a higher concentration of salts (chiefly) inside the cell, resulting in endosmosis across a semipermeable membrane.

The mechanism of irreversible swelling is at present less clearly understood. The outstanding fact as brought out by our experiments is that irreversible swelling is invariably associated with a profound change in the cell colloids, i. e., with permanent gelation or coagulation of the protoplasm. In addition, this process was found to have the following characteristics: First, it was repeatedly observed that the magnitude of swelling depended on the concentration or amount of the agent employed; second, coagulation generally, if not always, preceded

9. These toxins were obtained from the H. K. Mulford Laboratory.

swelling; and third, practically identical effects were produced by such widely different agents as hydrochloric and salicylic acids, ether, and heat.

There is, then, one kind of swelling that occurs in living cells, and another kind that occurs in dying or dead cells. Whether either or both of these processes are responsible for the swelling observed in cells of pathologic tissues cannot as yet be stated. It is to be expected, however, that such a general property of protoplasm as swelling will be similar in all kinds of cells.

SUMMARY AND CONCLUSIONS

Swelling was induced in isolated cells (unfertilized sea urchin eggs) by a number of agents of widely different nature.

Two types of swelling were distinguished. The first was induced by hypotonic solutions; within certain limits of length of exposure, concentration and temperature, such swelling was reversible, and not attended by injury to the cell.

The second type of swelling, produced by such diverse agents as hydrochloric acid, salicylic acid, ether and heat, was irreversible, and was attended by profound alteration of the colloidal state (irreversible gelation) and by death of the cell. In general, irreversible gelation preceded swelling.

The amount of volume increase was, as a rule, proportional to the concentration of the agent employed.

It is concluded that swelling of cells induced by acutely acting injurious agents is irreversible, indicates cell death and is due to absorption of water.

Whether this principle is also applicable to mammalian tissue cells, remains to be determined.

BLOOD SUGAR CHANGES RESULTING FROM INTRAVITAL INJECTIONS OF CERTAIN DYES*

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BOSTON

In previous experiments [1] showing the effect of intravenous injections of killed bacteria on the blood sugar level, the question arose as to the nature of the substances which may be effective in producing this type of hyperglycemia, and whether the reticulo-endothelial system, which reacts to the bacteria, might possibly play some rôle in the production of the associated hyperglycemia. In order to gain further data on the nature of substances which may induce an increase in blood sugar concentration, the effect of injecting other types of foreign material was determined. Vital dyes were employed with the thought that, in addition to involving the reticulo-endothelial system and exerting a chemical effect on the cells, possibly the distribution of the pigmented substance might give some clue as to the nature of the mechanism responsible for a resultant hyperglycemia.

A number of dyes were injected into animals, the effect on the glucose content of the blood determined, and the distribution of the dye observed. Blood sugar determinations were made at short intervals after a single injection, and in some cases the effect of repeated injections in the same animals was determined. Only dyes were used which are vital dyes in the sense that they are distributed through the animal body, penetrate cells and are of a low degree of toxicity.

EXPERIMENTAL PROCEDURE [2]

Rabbits and guinea-pigs were made to fast from eighteen to twenty-four hours in preparation for each experiment. The dyes were made up as 1 per cent solutions in physiologic sodium chloride solution. Guinea-pigs were used in preliminary experiments with each dye, to determine the distribution of the dye, its rate of absorption from the peritoneal cavity and route of elimination, and to determine the maximum dose per kilogram of body weight that was tolerated. Then the dye in a suitable dose was injected into rabbits. Before injection of the

* From the Department of Pathology of Harvard University Medical School and the Laboratory of Pathology, Long Island Hospital, Boston. Aided by a grant from the Proctor Fund of Harvard University.

1. Zeckwer, I. T., and Goodell, H.: Blood Sugar Studies: I. Rapid Alterations in the Blood Sugar Level of Rabbits as Result of Intravenous Injections of Killed Bacteria of Various Types, J. Exper. Med. **42**:43, 1925.

2. The dyes used in this work were used as obtained from the distributors and were not tested for purity.

dye and at short intervals thereafter, 1 cc. of blood was withdrawn from the ear veins, or occasionally by heart puncture, and blood sugar determinations carried out by the Folin-Wu method. The proteins were precipitated and filtration performed immediately after the blood was withdrawn. The filtrates were allowed to stand until about six specimens had accumulated, when they were run simultaneously against the same standards.

In most of the experiments the intraperitoneal method of injection was used, especially in the case of dyes which passed rapidly into the blood stream, as evidenced by the deep tinging of the cell-free blood serum. It was therefore possible to introduce the dye in dilute solution into the body without injecting a large amount of fluid into the blood stream directly. In some cases, however, the intravenous route was used in order to compare the effects with those after intraperitoneal injection. In some cases the hydrogen ion concentration of the solution was varied so as to prove that the effect on the blood sugar concentration was not due to the reaction of the solution.

For the structural formulas and chemistry of the dyes used in the following experiments, Michaelis,[3] Schultz and Julius,[4] or Allen [5] may be consulted.

Neutral Red.—Neutral red belongs to the azine group of dyes, and is a basic dye. The preparations used were "Neutral Rot zu Injekt. i. vital. Gew. n. Ehrlich." Grübler (prewar) and "Neutral Red Vital." Coleman and Bell.

Preliminary experiments were made on guinea-pigs, injecting intraperitoneally from 0.05 to 0.1 Gm. per kilogram of body weight as a 1 per cent solution in physiologic sodium chloride. A definite hyperglycemia resulted, reaching a maximum, at about one hour, of about 160 per cent increase over the original blood sugar concentration. The blood sugar curves were then more completely determined in rabbits. This rise in blood sugar was more pronounced than in guinea-pigs, often attaining values of from 200 to 280 per cent increase over the initial figures. The maximum values were reached usually from one-half to three hours after injection, and were followed by a rapid decline to normal in about six hours. The hyperglycemia was accompanied by glycosuria. Such a response to neutral red was invariable in all animals studied (table 1 and chart). Intravenous injections affect the blood sugar concentration in the same way as intraperitoneal injections.

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3. Michaelis, L.: Einführung in die Farbstoffchemie für Histologen, 1902.

4. Schultz, G., and Julius, P.: Tabellarische Uebersicht der im Handel Befindlichen künstlichen Organischen Farbstoffe, Berlin, 1897.

5. Allen: Commercial Organic Analysis, ed. 4, Philadelphia, P. Blakiston's Son Company **5,** 1912.

The dye when injected intraperitoneally is rapidly absorbed. In fifteen minutes the blood serum when acidified shows a deep tinging with red. The mucous membranes and skin of the ears appear definitely pink in from fifteen to thirty minutes. The usual symptoms after intraperitoneal injections are flushing of the vessels of the ears, increased blood pressure as evidenced by the rapid forcible flow of blood from a prick of the veins of the ear, increased force of the heart beat and increased respirations without any evidence of asphyxia. The rectal temperature usually falls and later returns to normal. The leukocytes fall immediately after injection, followed later by an increase. When the blood sugar is greatly elevated, the animals often become drowsy and sleep. In some animals these symptoms are scarcely noticeable. The degree of hyperglycemia does not appear to be proportional to the symptomatic manifestations. After intravenous injection of the dye these symptoms are not apparent, and yet the hyperglycemia may be of a high degree.

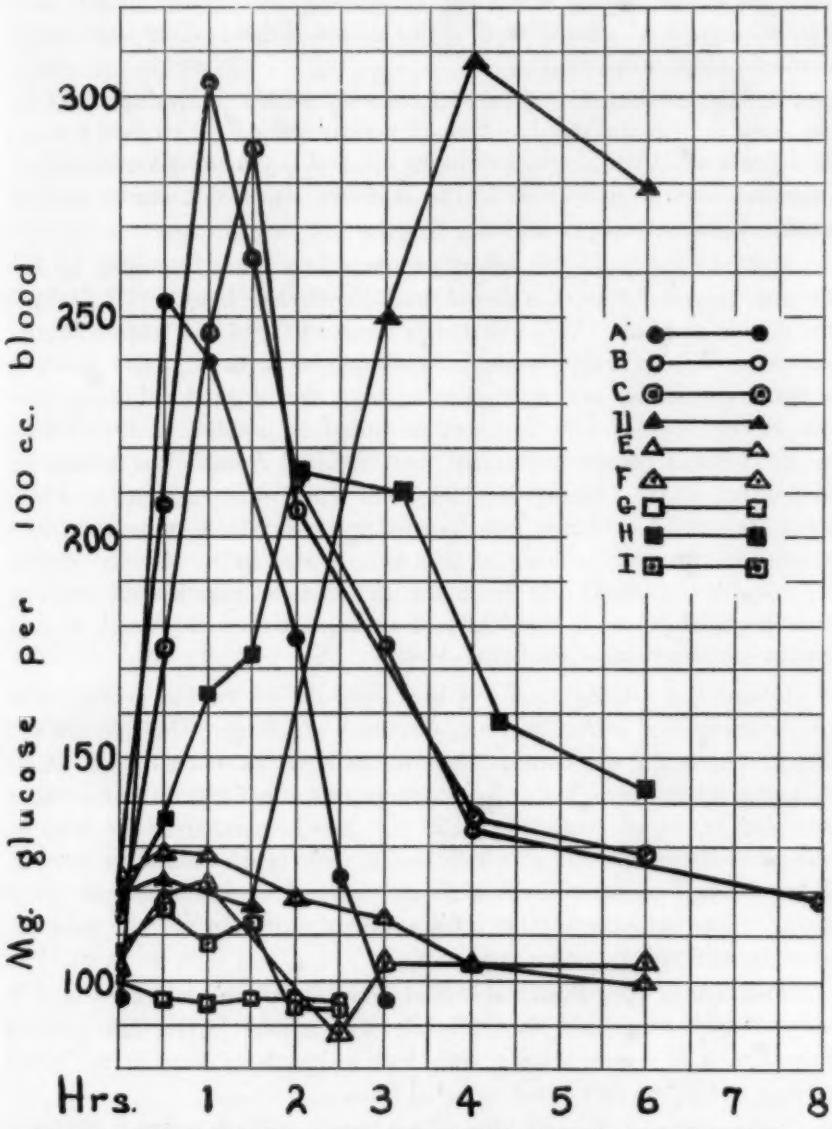
The distribution of the dye was studied in the unfixed tissue immediately after killing the animal. The dye is eliminated rapidly into the lumen of the stomach and small intestines, and into the bile and urine. In less than thirty minutes the dye stains diffusely all tissues. The deepest staining of the dyes, as seen grossly, is of the pancreas and the mucosa of the stomach and intestines. Histologically, aside from its appearance in the organs to which all foreign material is carried, it is especially characterized by its appearance in precipitate form as granules and needles in the acinar cells of the pancreas and the epithelial cells of the stomach and upper intestine. The dye is not stored to any extent in the reticulo-endothelial system, but is eliminated rapidly, only a slight amount of dye appearing after twenty-four hours. Since the dye changes to yellowish brown at hydrogen ion concentrations to the alkaline side of p_H 7.2, it is changed to this form several hours after injection except in those tissues which are acid.

Repeated doses of neutral red were given to some animals. There was no clear-cut difference in response to the dye on subsequent injections except as would be expected as a result of depletion of glycogen from previous injections. A permanent rise in the blood sugar never occurred. The animals tolerated the dye well, but after many injections lost weight. There were no gross or histologic lesions in any of the tissues as a result of single or repeated injections of the dye.

Safranin.—Safranin is an azonium base belonging to the same general group of dyes as neutral red. Two preparations were used, safranin (Grübler) and safranin Y (Coleman and Bell). When injected intraperitoneally into rabbits in doses of 0.045 Gm. per kilogram of body weight in salt solution, the blood sugar rose gradually, reaching values of from 50 to 155 per cent increase over the initial values.

Blood Sugar Values Following the Injection of Dyes

Animal	Date	Dye	Gm. Dye per Kg. Body Weight	Route of Injection	Mg. Glucose per 100 Cc. Blood									
					Before Injection	Hours After Injection								
						½	1	1½	2	2½	3+	4+	6+	8+
Rabbit 33....	2/17/26	Neutral red (Grübler).....	0.090	Intraperitoneal	104	229	...	177	...	130	...	...	125	...
Rabbit 32....	2/26/26	Neutral red (Grübler).....	0.080	Intraperitoneal	80	89	166	219	277	...	306	...	164	137
Rabbit 28....	12/ 2/25	Neutral red (Grübler).....	0.110	Intraperitoneal	95	210	173	115	...	...	...	...	106	...
Rabbit 34....	3/ 9/26	Neutral red (Grübler).....	0.075	Intraperitoneal	111	202	273	230	...	188	...	148	113	102
	4/19/26	Neutral red (Grübler).....	0.075	Intravenous	96	253	240	...	178	124	97	...	...	...
Rabbit 31....	2/ 7/26	Neutral red (Grübler).....	0.065	Intraperitoneal	121	208	303	263	212	...	177	134	...	119
	2/12/26	Neutral red (Grübler).....	0.065	Intraperitoneal	122	186	185	...	188	...	235	...	114	...
Rabbit 26....	10/19/25	Neutral red (Grübler).....	0.100	Intraperitoneal	99	223	145	...	...	...	110	91	...	...
	10/21/25	Neutral red (Grübler).....	0.085	Intraperitoneal	103	198	238	274	...	151	...	128	112	...
	10/26/25	Neutral red (Grübler).....	0.090	Intraperitoneal	122	135	153	187	168	...	125	98	71	...
	10/30/25	Neutral red (Grübler).....	0.090	Intraperitoneal	123	208	185	146	144	...	...	...	...	...
Dog 7.....	2/ 2/26	Neutral red (Grübler).....	0.037	.....	88	129	152	173	...	162	...	114	...	...
	3/ 3/26	Neutral red (Grübler).....	0.062	Intraperitoneal	80	...	158	...	190	198	...	...	...	...
Guinea-pig 35	9/25/25	Neutral red (Grübler).....	0.050	Intraperitoneal	90	...	...	...	...	...	...	157	...	...
	10/ 5/25	Neutral red (Grübler).....	0.050	Intraperitoneal	97	...	...	146	...	...	...	...	...	...
Guinea-pig 23	9/28/25	Neutral red (Grübler).....	0.050	Intraperitoneal	123	...	...	...	...	...	...	152	...	...
	10/ 2/25	Neutral red (Grübler).....	0.055	Intraperitoneal	101	...	...	131	...	...	...	...	...	...
Guinea-pig 33	11/20/25	Neutral red (Grübler).....	0.050	Intraperitoneal	119	157	...	192	...	...	...	...	...	...
Guinea-pig 38	12/ 7/25	Neutral red (Grübler).....	0.050	Intraperitoneal	115	...	165	...	...	...	...	...	...	...
Rabbit 42....	6/ 2/26	Neutral red..... (Coleman and Bell)	0.110	Intraperitoneal	100	168	185	160	...	133	...	106	103	...
Rabbit 45....	6/22/26	Neutral red..... (Coleman and Bell)	0.060	Intravenous	114	139	149	130	120	...	...	...	...	...
Rabbit 37....	4/19/26	Safranin (Grübler).....	0.045	Intraperitoneal	120	122	...	118	...	...	250	308	279	...
Rabbit 27....	10/ 2/25	Safranin (Grübler).....	0.045	Intraperitoneal	98	95	88	109	118	...	152	170	156	...
Rabbit 44....	6/15/26	Safranin Y..... (Coleman and Bell)	0.035	Intraperitoneal	104	109	103	113	...	105	121	134	130	...
Rabbit 38....	4/21/26	Congo red (Grübler).....	0.085	Intraperitoneal	113	175	247	289	206	...	...	137	129	...
Rabbit 41....	5/17/26	Congo red (Grübler).....	0.075	Intraperitoneal	102	122	147	169	163	160	140	118	103	...
Rabbit 43....	6/ 5/26	Congo red..... (Coleman and Bell)	0.065	Intraperitoneal	99	124	140	163	145	...	128	121	...	110
	6/16/26	Congo red..... (Coleman and Bell)	0.100	Intravenous	104	...	...	117	...	...	...	...	...	...
Rabbit 42....	6/15/26	Congo red..... (Coleman and Bell)	0.090	Intravenous	99	102	90	104	...	100	...	...	...	...
Rabbit 33....	3/19/26	Methylene blue B (Grübler)...	0.044	Intraperitoneal	105	178	188	168	150	...	147	...	106	...
Rabbit 29....	3/22/26	Methylene blue B (Grübler)...	0.068	Intraperitoneal	113	137	163	172	212	...	210	158	143	...
Rabbit 42....	5/19/26	Methylene blue vital..... (Coleman and Bell)	0.070	Intraperitoneal	105	119	109	112	97	97	...	...	...	...
Rabbit 7....	1/30/25	Trypan blue (Grübler).....	0.075	Intravenous	100	96	95	97	97	96	...	...	...	...
Rabbit 34....	3/17/26	Trypan blue (Grübler).....	0.074	Intraperitoneal	102	119	121	...	...	88	104	104	104	...
Rabbit 42....	4/29/26	Orange G..... (Coleman and Bell)	0.090	Intraperitoneal	122	129	128	...	119	121	113	104	100	...
Rabbit 43....	5/14/26	Bismarck brown..... (Coleman and Bell)	0.090	Intraperitoneal	108	124	122	111	111	107	108	105	85	...



Characteristic blood sugar curves following the injection of various dyes. *A* indicates the curve following the intravenous injection of neutral red into rabbit 34; *B*, intraperitoneal injection of neutral red into rabbit 31; *C*, intraperitoneal injection of congo red into rabbit 38; *D*, intraperitoneal injection of safranin into rabbit 37; *E*, intraperitoneal injection of orange *G* into rabbit 42; *F*, intraperitoneal injection of trypan blue into rabbit 34; *G*, intravenous injection of trypan blue into rabbit 7; *H*, intraperitoneal injection of methylene blue into rabbit 29; *I*, intraperitoneal injection of methylene blue vital into rabbit 42.

This dye is much more slowly absorbed than neutral red, and is very toxic, the animal becoming very weak and dying quietly with gradual cessation of respiration. On account of this toxicity, only a few determinations were made.

The dye cannot be traced satisfactorily within individual cells, as the color is pale and the dye diffuses rapidly out of the excised tissues. It is, however, definitely present in the bile and in the mucosa of the small intestine, and is eliminated by the kidney. It is not stored to any extent in the reticulo-endothelial system.

Methylene Blue.—The effect of methylene blue, belonging to the thiazine group of dyes, was determined. Methylene blue B (Grübler) is the double zinc salt. This injected in doses of 0.044 and 0.068 Gm. per kilogram of body weight caused a gradual rise in blood sugar reaching a maximum of 87 per cent increase over the original value in from one to two hours. This dye was discarded on account of its toxicity, as the animals became prostrated, with gradual cessation of breathing, and quiet death. Methylene blue vital (Coleman and Bell), which does not contain the zinc salt, had no pronounced effect on the blood sugar concentration in doses of 0.09 Gm. per kilogram of body weight. This dye is eliminated into the lumen of the stomach and small intestine and excreted through the bile and urine, and is not stored to any extent in the reticulo-endothelial system.

Congo Red.—Congo red is a benzidine dye of the azo group. The preparations used were Congorot (Grübler) and congo red (Coleman and Bell). After intraperitoneal injections in doses of from 0.05 to 0.085 Gm. per kilogram of body weight, there is a rapid rise in blood sugar reaching values of from 64 to 155 per cent increase over the original values in about one and one-half hours, with rapid decline to normal. Intravenous injections resulted in no pronounced effect on the blood sugar. The symptoms after intraperitoneal injection are the same as after neutral red.

This dye is very slowly absorbed from the peritoneal cavity and is very slowly eliminated through bile and urine. After intravenous injection, it is retained for a considerable length of time in the blood stream and in the reticulo-endothelial cells.

Trypan Blue.—Trypan blue (Grübler), an acid benzidine dye, was injected intraperitonelly or intravenously into rabbits in doses of 0.075 Gm. per kilogram of body weight. No pronounced changes in the blood sugar concentration resulted. "Blocking" the reticulo-endothelial cells by repeated injections in twelve guinea-pigs and two rabbits, with varying doses of dye and at varying intervals, had no effect on healthy animals. In two animals a rise of blood sugar occurred some hours after injection of the dye, and a high blood level was maintained for

many hours until the animals were killed. At necropsy it was found that these animals had infectious lesions in the lungs, and the increased number of phagocytic cells associated with this lesion had engulfed large quantities of the dye so that apparently an increased obstruction in the pulmonary ventilation had occurred with a resultant asphyxial type of hyperglycemia, which was maintained.

The retention of this dye in the cells of the reticulo-endothelial system is well known. It is present in the blood serum for many hours after injection, contrasting in this respect from such a dye as neutral red, which is in greatest concentration in the serum at the time of the highest point in the blood sugar curve but which is rapidly eliminated thereafter.

Other Dyes.—Dyes having no effect on the blood sugar concentration were Bismarck brown (vital, Coleman and Bell), orange G (vital, Coleman and Bell), phenolsulphonphthalein (Hynson, Westcott, and Dunning), and acid fuchsin (vital, Coleman and Bell). In the case of the last two dyes, only relative blood sugar values could be obtained as these dyes are not retained in the protein precipitate, as are all the other dyes used, but pass into the filtrate. To permit the making of relative determinations, the colors of the filtrates were adjusted to a uniform color by adding excess dyes in aqueous solution to each 2 cc. of filtrate in the paler tubes before adding the copper sulphate solution. These negative results served as controls for the positive results with other dyes.

Relation of Dyes to Proteolytic Enzymes.—Since it has been demonstrated that neutral red and safranin combine chemically in vitro with proteolytic enzymes, forming a colored precipitate which contains the enzyme (Brailsford-Robertson,[6] Marston,[7] Holzberg[8]), and since Epstein and Rosenthal[9] have suggested that proteolytic enzymes may play an important rôle in carbohydrate metabolism, the action of the various dyes used in the preceding experiments with trypsin in vitro was determined. Methylene blue was found to form a heavy flocculent colored precipitate when mixed with a clear solution of trypsin. The

6. Robertson, T. B.: Studies in the Chemistry of the Ion-Proteid Compounds: IV. On Some Chemical Properties of Casein and Their Possible Relation to the Chemical Behavior of Other Protein Bodies, with Especial Reference to Hydrolysis of Casein by Trypsin, J. Biol. Chem. **2**:343, 1907.

7. Marston, H. R.: The Azine and Azonium Compounds of the Proteolytic Enzymes, Biochem. J. **17**:851, 1923.

8. Holzberg, H. L.: A New Method of Isolating Trypsin, J. Biol. Chem. **14**:335, 1913.

9. Epstein, A. A., and Rosenthal, N.: Studies on the Relation of the External to the Internal Secretion of the Pancreas: II. The Effect of Trypsin on Insulin, and Its Bearing on the Causation of Diabetes, Am. J. Physiol. **71**:316, 1925.

character of the precipitate was similar to the precipitate formed with trypsin by neutral red and safranin. A precipitate was produced with Bismarck brown, but none of the other dyes formed precipitates.

Quantitative determinations of the proteolytic enzymes in the blood serum were made at short intervals after the injection of neutral red, coincidently with blood sugar determinations, in seven rabbits and one dog. Fluctuations in the enzymes titer occurred, but these were not constant and were considered to be due probably to other unavoidable factors.

COMMENT

The dyes of the azine group (neutral red and safranin) have several points in common: 1. They cause hyperglycemia. 2. They form a colored precipitate with solutions of trypsin in vitro. 3. They are eliminated into the lumen of stomach and intestine. 4. In the case of neutral red, the dye is seen in precipitate form as irregular granules and needles, in the cells forming proteolytic enzymes. In the case of safranin this is less easily ascertained, but its definite elimination into the lumen of the stomach and intestine indicates that these cells must contain the dye in large amounts.

Epstein with his co-workers,[9] in recent work tending to show that trypsin may neutralize insulin in the living body, injected safranin and neutral red among other substances directly into the portal vein, and compared the effect on the blood sugar with that resulting from the injection of the same substances into the arterial supply of the pancreas. He reports that trypsin and the dyes caused a rise in blood sugar when injected into the portal vein. When injected into the pancreas through the pancreatico-duodenal artery, the dyes caused no increase in blood sugar, while all other substances so introduced caused a rise in blood sugar. He accounts for this by saying that the dye fixes trypsin within the pancreatic cells, in view of the known in vitro reaction between safranin and trypsin; this fixation prevents the escape of trypsin into the blood, which, according to his hypothesis, would neutralize insulin.

In Epstein's work, anesthetics necessarily were used, namely, amytal, a derivative of barbituric acid, or ether. The effect of ether on the blood sugar is well known. Amytal was considered without effect on the blood sugar, but recently amytal has been reported to have a marked effect on carbohydrate metabolism,[10] and such has been my experience with this drug. The blood sugar curves in Epstein's experiments if plotted from his

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10. Weiss, S.: Anesthesia Induced by Barbituric Acid Deriviatives with Special Reference to Associated Blood Sugar Changes, Proc. Soc. Exper. Biol. & Med. **23**:363, 1926. Hines, H. M.; Boyd, J. D., and Leese, C. E.: The Effect of Amytal Anesthesia upon the Response to Intravenous Injection of Glucose, Am. J. Physiol. **76**:293, 1926.

figures will be seen to have irregular fluctuations, showing that the blood sugar level was being influenced by more than one factor. It therefore seems desirable that the effect of dyes in this relation be studied by other experimental methods. Aside from Epstein's work, no data on the effect of dyes on carbohydrate metabolism have been found in the literature.

That these dyes react with proteolytic enzymes may bear a relation to the fact that they cause hyperglycemia, but proof is lacking, since the results of quantitative determinations of enzymes were inconclusive.

The effect of Congo red seems to be quite different from that of neutral red. Hyperglycemia depends entirely on the direct contact of the dye with the peritoneal cavity and does not occur when the dye is injected into the blood stream.

The distribution of the dyes in the body gives no clue as to the mechanism by which hyperglycemia is produced. The dyes affecting the blood sugar are closely bound to proteins and are conspicuously excreted by the liver in the bile and are excreted by the gastro-intestinal tract, but other dyes not affecting the blood sugar have the same characteristics. The exact localization of the dyes in the tissue is difficult to determine with accuracy, except in the case of trypan blue, as in making permanent sections the dyes dissolve out in the alcohols.

Examination of the fresh tissue in frozen sections or teased preparations was also unsatisfactory, as one can never be certain that one is not seeing the effect of supravital staining of granules, due to the excess dye in the tissue fluids staining structures in the cell that is no longer living, rather than the effect of true vital staining.

The dyes used were as far as possible those prepared especially for vital staining. Presumably impurities are in negligible amounts, but the possibility remains that some impurity rather than the dye itself is responsible for the hyperglycemia. Two different manufacturer's products were used to guard against the possibility that a given impurity was present in any one sample of dye. There are few data on hand in the literature to indicate what type of impurities may be present in dyes, except that it is known that metallic salts may be present in traces. The literature on the effect of metals and metallic salts on the blood sugar is scanty. Van Dyke[11] has found that 1.9 mg. sodium arsenite per kilogram of body weight in the rabbit induces a hyperglycemia of about the grade occurring in the present experiments with dyes. If arsenic were responsible for the effect of the dyes, it would have to be present in the dry dye in amounts of about 2 to 4 per cent, which is in excess of the amount that would be expected as an impurity in a dye. The literature on the effect of metallic salts in producing

11. Van Dyke, H. B.: Effect of Sodium Arsenite on Blood Sugar Concentration of Rabbit and Dog, J. Pharmacol. & Exper. Therap. **26**:259, 1925.

glycosuria is reviewed by Salant and Wise.[12] Apparently when these substances produce glycosuria, it is dependent on definite injury to the kidney. The glycosuria does not develop until many hours or sometimes several days have elapsed since the injection, and the glycosuria persists for a long time. Evidently dyes produce an entirely different type of glycosuria, and no gross or microscopic lesions of the kidneys were ever found as a result of single or repeated injections of dye.

The rise in blood sugar is probably not due to decreased insulin activity, as the rise is too rapid and of too great a magnitude to be the result merely of failure in the utilization of the amount of glucose that is normally present in the blood stream. Furthermore, neutral red has no direct reaction with insulin in vitro, as when the dye was mixed with insulin and allowed to stand and the clear mixture later injected into animals, the insulin effect was unaltered, the curve of blood sugar being such as would be expected as a balance between the hyperglycemic effect of the dye and the hypoglycemic effect of insulin. There must, then, be an increased discharge of sugar into the blood stream. Whether this hyperglycogenolysis is the result of the dye acting directly on the liver cells, or whether it is accomplished through the mechanism of the autonomic nervous system, remains to be determined. The conspicuous presence in the bile of those dyes affecting the blood sugar level suggests that direct action of the dye on the liver cell is a possibility.

The curves of blood sugar bear a remarkable similarity to the curves obtained after intravenous injections of killed bacteria of various types, the maximum blood sugar values being much the same, and the period of rise and fall being of about the same duration. The general systemic reactions of the animals, however, contrasted markedly. After bacterial injections, the blood pressure falls, the ear vessels are constricted and the animal is weak and often prostrated. After dyes there may be no symptoms, or the blood pressure may be considerably raised, the ear vessels dilated, the heart beat increased in rate and force, and the animals lively. After toxic doses of dyes such as safranin, the symptoms may be more like those following bacterial injections.

Since these changes in the blood sugar concentration result from the injection of foreign particulate matter, the possibility that the reticuloendothelial system may play a rôle was considered. As multiple activities have been attributed to these cells aside from phagocytosis, such as transformation of hemoglobin into bilirubin, production of hemolysins to foreign red cells, of antitoxins, of complement, and formation of fibrin, these cells perhaps play a larger rôle in chemical and physiologic processes than is ordinarily supposed. Furthermore, insulin has been

12. Salant, W., and Wise, L. E.: The Production of Glycosuria by Zinc Salts, J. Biol. Chem. **34**:447, 1918.

reported to have been recovered in fair amounts from the spleen and liver, which are rich in reticulo-endothelial cells. Obviously these cells are involved after injection of bacteria and dyes. However, "blocking" these cells with trypan blue, which presumably alters their function, produced no changes in the blood sugar except when the lungs were so loaded with dye, due to an abnormal number of reticulo-endothelial cells secondary to an infectious lesion, that a mechanical obstruction occurred to aeration of the lungs and a resultant asphyxial type of hyperglycemia at a more or less permanent level. The dyes most effective in raising the blood sugar are not retained by the reticulo-endothelial cells to any extent.

The effect of the dyes on the blood sugar is not without practical significance, as these dyes have been used in human beings as clinical tests (Schönberger and Rosenblatt,[13] Bennhold,[14] Piersol, Bockus and Bank,[15] Glaessner and Wittgenstein,[16] Saxl and Scherff,[17] Davidson, Wilcox and Haagensen,[18] Carnot and Gaehlinger,[19] and others.

SUMMARY

1. Injections into animals of neutral red and safranin invariably result in a rapid rise in the blood sugar concentration to a high level with decline to normal in a few hours. Glycosuria accompanies the hyperglycemia. Congo red when injected intraperitoneally causes a transient hyperglycemia. Orange G, Bismarck brown, acid fuchsin, and phenolsulphonphthalein do not affect the blood sugar concentration.

2. The fact that neutral red and safranin appear to combine with proteolytic enzymes within the cell body may bear a relation to the blood sugar changes, but proof for this is wanting.

3. The blood sugar curves after dyes are similar in character to the curves following injections of killed bacteria of certain types, and probably in both cases are the result of hyperglycogenolysis.

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13. Schönberger, E., and Rosenblatt, J.: Ueber intravenose Kongorot injektionen nach Bennhold, Wien. klin. Wchnschr. **38**:1113, 1925.

14. Bennhold, H.: Ueber die beziehung des Kongorotes zur Amyloiden Substanz und über den Mechanismus der Beschleumigten Farbstoffausscheidung bei tubulären Nierenkrankheiten, Klin. Wchnschr. **3**:1711, 1924.

15. Piersol, G. M.; Bockus, H. L., and Bank, J.: Practical Value of Neutral Red Test for Gastric Secretory Function, Am. J. M. Sc. **170**:405, 1925.

16. Glaessner, K., and Wittgenstein, H.: Ein neuer Weg zur Funktionsprüfung des gesunden und kranken Magens, Klin. Wchnschr. **2**:1650, 1923; Ueber die Ausscheidung vom Farbstoffen durch den Magensaft, Wien. klin. Wchnschr. **36**:732, 1923.

17. Saxl, P., and Scherff, D.: Erwiderung auf obige Bemerkung (Glaessner und Wittgenstein), Wien. klin. Wchnschr. **36**:732, 1923.

18. Davidson, P. B.; Wilcox, S., and Haagensen, C. D.: Gastric Excretion of Neutral Red, J. A. M. A. **85**:794 (Sept. 12) 1925.

19. Carnot, P., and Gaehlinger, H.: Une nouvelle méthode d'appréciation de la sécrétion stomacale: la chromoscopie gastrique, Paris méd. **2**:377, 1924.

Laboratory and Technical Notes

WASSERMANN VS. FLOCCULATION TESTS IN THE SEROLOGIC STUDY OF SYPHILIS

Suitability of Kahn Test as an Office Procedure

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ATLANTIC CITY HOSPITAL, ATLANTIC CITY, N. J.

The complexity of the Wassermann test, and the equipment and training required for its reliable performance have restricted this procedure to the serologic laboratory. Therefore endeavors have been made to devise some simpler and shorter test.

The treatment of syphilis is a tedious matter; there is, therefore, no necessity for procedures requiring minutes rather than hours. Hence the time involved does not make it necessary to replace the Wassermann test. The complexities of the test, however, render it liable to technical errors; on the other hand, this very complexity tends to restrict its performance to those skilled in serologic procedures.

I shall not discuss the significance or interpretation of the Wassermann reaction in syphilis. This procedure has undergone intensive study since its introduction in 1906; and earlier and erroneous conceptions relating to the incidence and significance of positive reactions have been corrected. By means of various technical refinements, its delicacy and relative specificity have been vastly enhanced; and the critical studies of twenty years and the hypercritical analysis of millions of tests have established the status of the reaction as the most delicate and constant *single* symptom of syphilis.

From time to time, simplified procedures have been proposed in its place, all based on the colloidal lability of blood serum in general and of syphilitic serum in particular by reason of which flocculation may be produced by a variety of colloidal solutions. Prominent among these tests at the present time is that proposed by Kahn.[1]

I am not concerned with the relative specificity or general reliability of this procedure when carefully and properly performed, but with various impressions which have gained circulation and which require discussion.

A number of physicians regard the Kahn test not only as a *specific* method for the serologic diagnosis of syphilis, but also—and this is the particular point at issue—as an exceedingly simple method which requires neither skill, nor equipment, and which is safe in the hands of the average office attendant.

Such statements appear in the current literature. It seems desirable, therefore, to consider, first, the suitability of the Kahn test as an *exclusive* method for the serologic diagnosis of syphilis; and, second, its suitability as an office procedure.

The two essentials of any serologic method of diagnosis in syphilis are delicacy and relative specificity. The status of the Wassermann test in rela-

1. Kahn, R. L.: Serum Diagnosis of Syphilis by Precipitation, ed. 1, Baltimore, Williams & Wilkins Company.

tion to these requirements when properly performed by a reliable method and a skilled serologist is now well established.

It may be accepted that:

1. The Kahn test is much more delicate and reliable than the Sachs-Georgi test, of which it is a modification.

2. The Kahn test checks with the Wassermann reaction in from 80 to 90 per cent of cases, depending on the care with which it is performed and the delicacy and reliability of the Wassermann technic with which it is compared.

3. Both false negative and false positive reactions occur with the Kahn test.

4. The Kahn test is unsatisfactory and unreliable with spinal fluids.

5. The ring test modification is neither as delicate nor as reliable as the original technic.

6. The micromethod, using infinitesimal quantities of reagents on glass slides, the results being read under the microscope or by the naked eye, is a highly dangerous procedure except — and even perhaps — in the hands of well trained serologic workers. As an experiment, it is of interest; as a method for the diagnosis of syphilis, it should be condemned.

The adoption of the Kahn test as the sole means for the serologic diagnosis of syphilis by the laboratories of a state board of health and by the navy has been widely heralded as establishing its general suitability for this purpose. The fact that the originator of the test is director of the state laboratories in which the test has replaced the Wassermann test is of some significance in this connection. The difficulties involved in the satisfactory performance of Wassermann tests aboard ship or in isolated naval stations, and the fact that all naval surgeons are not necessarily accomplished serologists, must influence its adoption.

That the Kahn test is an absolutely specific procedure for the diagnosis of syphilis, remains to be proved; that it is a procedure requiring neither skill nor training for its reliable performance, can be denied emphatically.

Although widely heralded as a method of extreme simplicity, the Kahn test introduces its own technical difficulties, and these are of no small moment in influencing the delicacy and especially the specificity of the results.

In the first place, the preparation of a suitable antigen is difficult. The preliminary titration to determine the most suitable concentration for use in the test is of great importance, and should be done at frequent intervals in order to avoid fallacious results due to changes in antigenic titer. A worker incapable of preparing and titrating his own reagents is unfitted for the performance of serologic tests.

In the second place, the Kahn test requires the *accurate* pipetting of extremely small quantities of serum and antigen, and this alone demands skill attainable only by practice.

Consistent accuracy in this step is of primary importance, for both the delicacy and relative specificity of the reactions are directly and profoundly influenced by variations in the concentrations of serum and antigen. So important is this factor that Kahn recommends that not more than ten tests be set up at one time, even by the skilled worker, in order to avoid introducing variations in concentration by evaporation of the small amounts of reagents involved.

In the third place, and of marked importance, since the borderline weak reactions are often difficult to read and interpret, and the clinical evidence in these cases is least reliable, serologic methods should be most reliable and least open to misinterpretation.

The relative specificity of the Kahn test is still a matter subjudice.

There are differences in the relative colloidal stability of normal and syphilitic serums on which all flocculation tests depend. It remains to be proved, however, that these differences are due to the presence of specific substances specifically precipitable by the flocculating agent; that the Kahn antigen is specific in this respect; or that flocculation cannot be obtained in normal or nonsyphilitic serums, or missed in syphilitic serums by any flocculation test yet devised.

In any consideration of methods of serodiagnosis in syphilis certain essentially important facts must be remembered:

First, there are men for whom a serologic positive reaction means syphilis, and vice versa; second, it follows, therefore, in any procedure, that relative specificity is the most important attribute in conjunction with delicacy.

While the Kahn test may be accepted as more sensitive than many, if not all, of the flocculation tests hitherto described, its specificity is affected by many factors, and its comparative sensitivity is definitely influenced by that of the Wassermann technic with which it is compared. It is, for example, neither more sensitive, nor more specific than some of the newer Wassermann methods, such as Kolmer's.

At times, the Kahn test remains positive longer in treated syphilis than the Wassermann test. The clinical significance of such reactions, however, remains to be determined.

That the Kahn test is a safe or reliable procedure in the hands of the average office attendant, is to be vehemently denied. If it is so regarded, the erroneous diagnosis of syphilis will be made with inexcusable frequency because of false reactions attributable both to imperfections of technic and to misinterpretation of results. It is far easier to train technicians to perform reliable Wassermann tests than equally reliable Kahn tests.

CONCLUSIONS

The Kahn test is a safe and reliable procedure only in the hands of skilled workers trained in serologic manipulations.

It should be used in conjunction with and not in the place of the Wassermann test.

It is unsuited for the rapid serologic diagnosis of syphilis in the office of the physician at large.

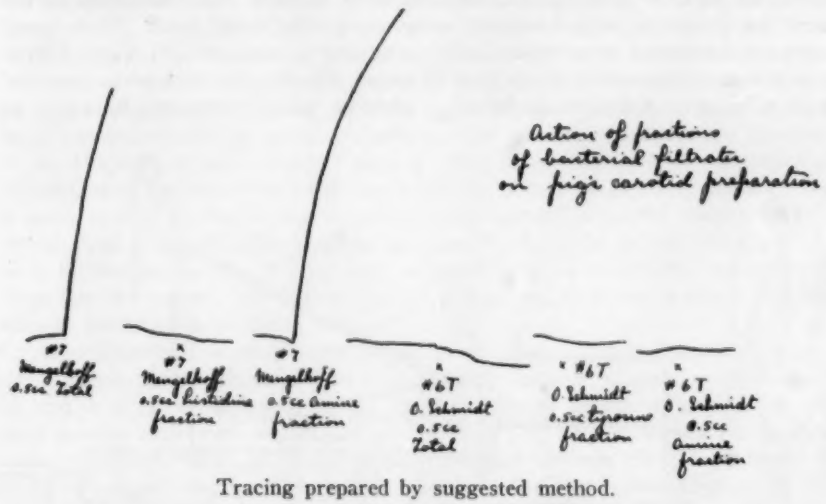
THE PREPARATION OF KYMOGRAPHIC TRACINGS FOR PHOTOGRAPHING*

JULIAN H. LEWIS, M.D., CHICAGO

Kymographic tracings on smoked paper are difficult to photograph in the preparation of plates for publication and for lantern slides. The tracings consist of fine white lines on an intensely black background which do not register satisfactorily on a photographic plate. Moreover, the white lines are often obscured by the solution used to fix the tracings, whether it be white shellac, gum damar or any other substance, because these usually impart some color to the white paper and cut down the contrast between the white lines

*From the Otho S. A. Sprague Memorial Institute and the Department of Pathology, University of Chicago.

and black background. If the tracings are such as to give a mass effect of white lines the results are better because the contour of the whole curve is given; but with tracings consisting of isolated lines it as almost impossible to make plates that show them distinctly. Having a large number of the latter kind of tracings on hand to be photographed, we resorted to a method of reproduction which has given excellent results. It consists of tracings with black India ink on white paper. A box covered with a piece of glass is illuminated on the inside with a rather strong light. The tracings are placed on the glass plate and over them a sheet of ordinary white typewriter paper. The white lines of the tracing are clearly seen on the latter and are carefully traced with a sharp



Tracing prepared by suggested method.

lead pencil. After tracing with the lead pencil, the lines are gone over with a fine pen and India ink. The net result is that the curve consists of black lines on a white background, and the lines, if necessary, can be made heavier than the original tracing without disturbing the accuracy of the record. This method furnishes a finished product that is much easier to photograph, and, in addition, blurs and unnecessary portions of the original curves can be eliminated at will, and groupings made that were not possible when the tracings were produced.

The figure shows a tracing prepared by this method.

SIMPLE FOUR-VALVE APPARATUS FOR DETERMINATION OF TOTAL RESPIRATORY METABOLISM IN SMALL ANIMALS*

KAMIL SCHULHOF, M.D., CHICAGO

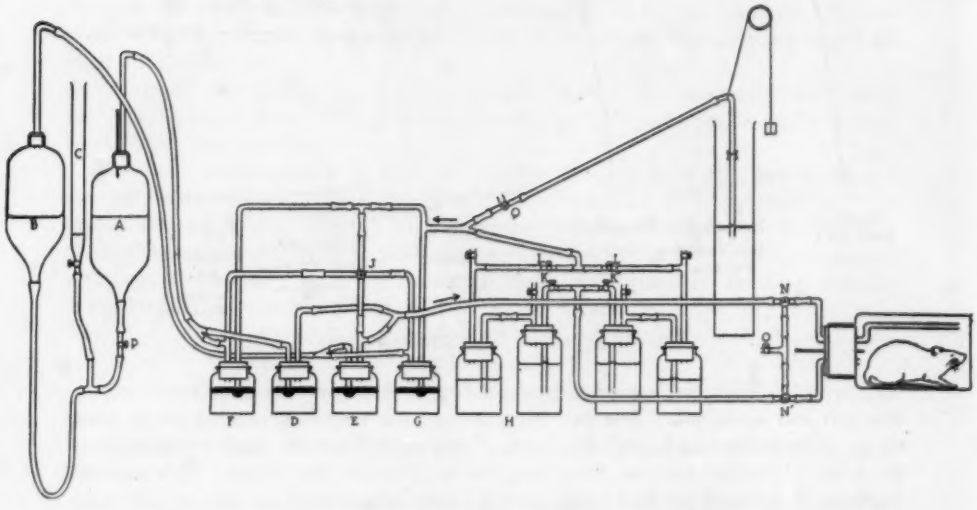
The following is a description of an apparatus for the determination of respiratory metabolism in small animals, which might be useful in laboratories that are working chiefly on other problems and therefore are not inclined to acquire an expensive device. It is especially applicable, if several experiments are being made at the same time, each requiring a separate apparatus. It is

*From the John McCormick Memorial Institute for Infectious Diseases.

always desirable to be able to determine the carbon dioxide production as well as the oxygen consumption, because each checks up on the other and because the respiratory quotient is acquiring a new importance. For such purposes gas analysis has been practically universal so far. It requires not only an expensive apparatus and special skill, but also a great deal of actual time-consuming work. The latter factor has lead to the devising of a different apparatus which for several months has given satisfactory results.

It may be constructed in a few hours at a negligible expense, and any one familiar with simple laboratory procedures has no difficulty in learning how to use it.

In the figures, *A* and *B* are bottles holding about 1 liter each, such as are used for irrigation with a surgical solution of chlorinated soda. Their lower ends are connected by a rubber hose containing a stopcock (*P*) which allows regulation or interruption of the flow of water. Besides this the hose is connected with a buret or a separatory funnel *C*, through which water may be added or



withdrawn from the system. As a rule, one of the bottles and the rubber tubing are almost filled with acidified water or mineral oil. Bottle *A* contains a thermometer and is fixed, while bottle *B* may be moved up and down. The upper openings of the bottles are closed by rubber stoppers containing a glass tube at least 35 cm. long. With a flow of 1 liter a minute it is evident that bottle *B* has to be raised or lowered only about once a minute, which is not difficult to do manually, although a mechanical device may be used instead.

J is a four way stopcock (the two borings crossing in the same plane). When open, it allows free communication of air between the tubes connected with it. When turned 45 degrees, the communication is interrupted. Bottles *D*, *E*, *F* and *G* are mercury valves. The lower part of these bottles is filled with solid paraffin. In every valve two glass tubes pass through a rubber stopper; one of them ends above the mercury, the other just touches it. It is unnecessary to immerse it deeper. Water valves may be used instead, but they require a much longer tubing. The bottles as well as all the connections on the apparatus are made air tight by a mass of gelatin. *M* is a spirometer—in this case a graduated buret holding 100 cc., and immersed in water. This arrangement is

more convenient than a manometer consisting of two burets. *Q* is a three-way stopcock, through which oxygen may be refilled. The pairs of stopcocks *K, L* and *K', L* lead to two sets of absorption bottles. With barium hydrate three bottles connected in a series are necessary. With potassium hydrate two are sufficient. The three way stopcocks *N* and *N'* lead the current of air either through the animal chamber or through a short circuit which may be opened to the room air or serve for filling the apparatus with oxygen, unless stopcock *Q* is used for this purpose. The latter is preferable, since the air may be kept moving around the animal during refilling.

When bottle *B* is raised and the water flows from *B* to *A*, it aspirates the air into *B* and drives it from *A*. The air current passes from *A* to *D, N*, animal chamber, *N', K, H, L, G, B*. When the bottle *A* is raised, the air flows from *B* to *E, N*, animal chamber, *N', K, H, L, F, A*. It is evident that this arrangement ensures a flow of air interrupted only for a fraction of a second during the raising or lowering of a bottle. Furthermore, the valves direct the air current in one way through the animal chamber and the alkaline solution, thus ensuring a good airing of the chamber and an immediate as well as quantitative absorption of carbon dioxide. A much smaller volume of gas, and consequently a much smaller correction for changes of temperature, is needed because of this device than if the air were floating back and forth in the animal chamber. In fact, the bottles holding 1 liter were selected only to lessen the frequency of lowering and raising the bottles. With a mechanical device a much smaller volume would be sufficient.

Absorption bottles could serve instead of the valves *F* and *G*, and originally did. Concentrated sulphuric acid may be used instead of mercury in bottles *D* and *E* if it is desirable to dry the air coming to the animal. Yet the arrangement described was found preferable. The air coming to the animal may be partially dried by inserting a bottle with calcium chloride between *N* and the animal chamber. As a rule, however, the higher temperature in the animal chamber prevents the complete saturation of the passing air with water vapor.

A 500 cc. bottle with a broad neck serves as animal chamber for rats. A rubber stopper containing two glass tubes and a thermometer protected by a wire net fits in it.

Test for Leaks: The stopcocks *N* and *N'* should be opened both to the animal chamber and to the stopcock *O* or *Q* which is opened to the room air. All the other stopcocks should be opened, and the manometer *M* immersed in the water. Stopcock *O* or *Q* should be closed, and the buret *M* raised above the water surface. Some of the water will run out, then the flow stops, if there are no leaks. Only a drop will fall now and then because of changes of temperature in the system. The difference in pressure thus obtained is much larger than any change which will occur during the experiment, if the level in the buret is kept reasonably near that of the surrounding water. Tests for leaks should always be made before and after the experiment.

Experiment: Stopcocks *J* and *O* should be opened. The stopcocks to one set of absorption bottles, for instance *K* and *L* should be opened, and stopcocks *K'* and *L'* closed. The animal is put into the chamber, stopper inserted and the temperature of the chamber read when closing the stopcock *O*. Stopcock *J* should be closed by turning it 45 degrees, the temperature in bottle *A* read and bottle *B* raised.

When the reading is being taken it is advisable to raise bottle *B* about twenty seconds in advance. The temperature of the animal chamber and of bottle

A should then be read. The time should be read when opening stopcock *J*. On the opening of this stopcock the air current through the animal chamber stops, the air taking a shorter circuit between *A* and *B*, and the pressure in the valves is equalized. After opening stopcock *J*, it is of advantage to close the stopcock in the water hose connecting bottles *A* and *B*. The introduction of stopcock *J*, as well as the direction of the air current in one way by means of the four valves, constitute, in my opinion, the two main technical advantages of the apparatus.

It has not been found necessary to equalize the pressure in the absorption bottles. It is easy to do this, but the more stopcocks used, the more greasing and the more possibilities for leaks. After opening the stopcock *J*, which stops the circulation of air around the animal, and closing stopcock *P* (in the water hose connecting *A* and *B*), the manometer is raised or lowered until the level of water in it is identical with the surrounding water, and the reading is made. If one wishes to change the absorption bottles for determination of carbon dioxide produced in the preceding period, the oxygen consumption is read as described, then stopcocks *K* and *L* are closed (always with open stopcock *J* and manometer on the level with the external water), and *K'* and *L'* are opened. The time noted for carbon dioxide is also that which was recorded on the opening of stopcock *J*, since no air had passed through the animal chamber after that time. The slight accumulation of carbon dioxide and loss of oxygen in the animal chamber occurring while the reading is being made does not cause an error—the whole procedure takes rather less than a minute. To avoid a slight source of error stopcocks *N* and *N'* may be turned off the animal to the short circut after opening stopcock *J*, but it is not necessary.

Even readings taken as frequently as every five minutes check well, as a rule, although I use longer periods (from fifteen to thirty minutes) for the experiment. The absorption bottles may be emptied and refilled several times during the experiment. To avoid compression of air, two of the tubes leading from the bottles are left open until the stoppers are tightly in place. Oxygen may be refilled through *Q* after closing stopcock *Q* from the system or through *O* after closing the stopcock *N* and *N'* from the animal at any time, or if the whole apparatus has been filled with oxygen, a corresponding amount of water may be used to replace the consumed oxygen. The separatory funnel *C* serves for this purpose. No short circuiting is necessary with the latter method, which is essential for special purposes, such as metabolism determinations under decreasing oxygen pressure.

The temperature of the system changes so little that it is hardly worth while to measure the temperature of the water for correction. The volume of the animal chamber is 500 cc. Subtracting the weight of the animal from this gives a reasonable basis for the actual volume and correction for this part of the apparatus (0.5 per cent per degree centigrade and 100 cc. of air). The volume of gas in the rest of the apparatus may be estimated according to the diameter and length of the tubing and the air content of the valves and bottles.

The carbon dioxide may be determined by titration of a definite portion of the filtered contents of the washing bottles. I fill them with 250 cc. of an approximately half or third saturated solution of barium hydrate, the first bottle of the series containing about 150 cc., and the second and third the rest. About 50 cc. of distilled water may be used to wash the bottles and increase the volume to 300 cc. before titration. Either the solution of hydrochloric acid used for titration may be prepared so that 1 cc. corresponds to 1 cc. of carbon dioxide at 0 C. and 760 mm. mercury (898.8 cc. of tenth

normal solution of hydrochloric acid is used and filled up to 1 liter of water), or any solution of hydrochloric acid may be taken and titrated against 89.88 cc. of a tenth normal alkali solution. Every cubic centimeter of this solution of hydrochloric acid corresponds to $\frac{}{a}$ cc. of carbon dioxide at reduced temperature and pressure, a being the number of cubic centimeters of the acid necessary to neutralize the 89.88 cc. of tenth normal alkali. Determination of specific gravity may be used also instead of titration in determining the carbon dioxide production.

The variations in pressure occurring during the raising and lowering of bottle *B* do not impair the results in any way as long as the animal is enclosed in a chamber. They are not strong enough to irritate the animal; if they were stronger and more frequent, they would make the gas exchange of the animal easier: the respiratory movements become superfluous with continuous rhythmic changes in pressure, as discovered and utilized by Thunberg in his ingenious barospirator. However, the changes in pressure would constitute a serious disadvantage if only a mask were used while the atmospheric pressure acted externally on the chest. In case a mask is used, this difficulty may be overcome by inserting in the expiratory tube a rubber bag enclosed in a bottle which communicates with the tube carrying air to the animal. An additional communication of this air with the air coming from the rubber bag to the absorption bottles may be added, if the animal is strong enough to breathe through valves. This device is easily adaptable for the determination of the total metabolism in man, when an air pump is used. For small animals, such as rabbits, the pressure may be equalized by two rubber bags open to room air and enclosed in air tight bottles communicating with the mask, as will be described elsewhere. However, these accessories are superfluous, if the animal, whether a rat or a rabbit, is enclosed in a chamber.

The possibility of exact determination of the rat's metabolism at shorter intervals has a great advantage: Those parts which are changed by the occasional restlessness of the animal can be disregarded. In the usual determinations lasting for from three to six hours such periods increase the basal rate and render the method less sensitive than it could be. It is also a mistake to assume that the metabolism reaches its minimum shortly after the preliminary half hour. Its course is illustrated by the following table reporting a determination of metabolism made on a rat weighing 205.5 Gm.—about the largest size which may be tested in a 500 cc. bottle. It will be noted that the slight movement at 3:49 immediately increased the oxygen consumption from 3.81 to 4.05 a minute (by 6.3 per cent). If a continuous determination began at 3:28 (forty-three minutes after the animal had been put into the bottle), the average oxygen consumption a minute would be 3.94 cc. It is evident that a lower figure—about 3.80—is more correct. Slight as the difference may be in this case (3.5 per cent), it is in favor of the method I described. In other experiments the difference is much greater; in other animals, the oxygen consumption is almost constant. A strong solution of hydrochloric acid (1 cc. corresponding to about 10 cc. of carbon dioxide) was used for titration; hence the differences in the respiratory quotient.

The metabolism was figured as follows:

For instance, at 3:11 the spirometer was refilled to 100 cc., while the temperature of the animal chamber was 27.3 C. and the temperature of the rest of the air in the apparatus was 25.6 C. At 3:28 the next reading (4.6) was taken, the temperature of the chamber having risen to 25.7 C. and the temperature of the system fallen to 25.4 C.

The preliminary correction for the changes in temperature of the animal chamber is 1.5 cc. per degree centigrade (0.5 per cent of the volume of air in the chamber—500 cc. minus approximate weight of the animal which is about 200 Gm.). The volume of air in the rest of the system was 1,800 cc., the correction being therefore 9 cc. per degree centigrade. If it is decided to make the preliminary correction to 25.4 C., $(27.3 - 25.4) \times 1.5 = 2.85$ cc. must be

Determination of Respiratory Metabolism of Male Rat Weighing 205.5 Gm.; Barometric Pressure 747 mm.

Time	Temperature of Animal Chamber	Temperature of Air in System	Spirometer Reading in Cc.	Gross Difference in Oxygen	Oxygen Consumption at Reduced Temperature and Pressure	Carbon Dioxide at Reduced Temperature and Pressure	Respiratory Quotient	Oxygen Consumption per Minute	
2:45	25.6	25.7	100.0	....	....	....	.....	....	Animal washes
2:56	27.1	25.6	5.0	95.0	84.6	....	.....	7.62	Animal quiet
			100.0	....	....	102.0	0.764	....	Spirometer refilled to 100 cc. mark
2:58	....	....	....	....	....	....	.....	....	Animal washes, then quiet
3:04	27.3	25.6	44.4	55.6	49.3	....	.....	6.16	
									Change to second set of absorption bottles
3:11	27.3	25.6	5.4	39.0	32.9	92.1	0.806	5.43	Animal washes, then quiet
			100.0	....	....	....	.....	....	Spirometer refilled
3:28	27.5	25.4	4.6	95.4	81.4	....	.....	4.78	
			100.0	....	....	....	.....	....	Spirometer refilled, change to third set of absorption bottles
3:34	27.3	25.4	70.6	29.4	25.2	....	.....	4.20	Animal quiet
3:42	27.3	25.4	34.2	36.4	31.52	71.5	0.821	3.94	
3:49	....	....	....	....	....	....	.....	....	Animal moves slightly
3:50	27.3	25.4	—1	35.2	30.5	....	.....	3.81	
			100.0	....	....	....	.....	....	Spirometer refilled, change to third set of absorption bottles
3:51	....	....	....	....	....	....	.....	....	A few jerky breaths, then quiet
3:55	27.3	25.4	76.6	23.4	20.25	....	.....	4.05	Animal quiet
4:05	27.2	25.4	31.0	45.6	39.3	....	.....	3.93	
4:11	27.15	25.4	4.6	26.4	22.75	....	.....	3.79	Animal removed. No leak in apparatus

substracted for the chamber, and $(25.6 - 25.4) \times 9 = 1.8$ cc. for the remaining system. The result was 95.3 instead of the first spirometer reading of 100. In a similar way the second spirometer reading of 4.6 was corrected to 1.4 by subtracting from it $(27.5 - 25.4) \times 1.5 = 3.2$ cc. Thus instead of the gross difference of 95.4, the correct difference of 93.9 of moist oxygen at 25.4 C. and 747 mm. mercury was obtained.

This volume was reduced to dry gas volume at 0 C. and 760 mm. of mercury by multiplying with the factor 0.866. The logarithms of these factors may be found in Boothby and Sandiford's book, although I found it preferable to make

from these tables a graph in which the abscissas represent temperature, the ordinates, the number of these logarithms. The graph is obliquely crossed by the lines representing barometric pressures. The reduction factor may be obtained from such a graph at a glance, and the correct volume is found by the slide rule.

SUMMARY

1. A four-valve apparatus for the determination of respiratory metabolism in small animals is described, which may be set up easily in any laboratory and does not require any special skill.

2. Without a mechanical driving device, it leads the air current one way and practically continuously through the animal chamber, and causes it to bubble through an alkali solution. Thus a quantitative absorption and determination of carbon dioxide is ensured in an indefinite series, and a similar uninterrupted series of determinations of oxygen consumption may be made at intervals chosen by the worker at any stage of the experiment. The latter feature eliminates the errors arising from occasional restlessness of the animal, because the corresponding parts of the metabolism curve may be disregarded.

3. The one way current does away with the necessity of using large amounts of air in the system and the large corrections for changes in temperature resulting from this.

General Review

THE PRESENT STATUS OF CORONARY ARTERIAL DISEASE *

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We might begin by quoting from Marshall Hall's noted Gulstonian Lectures for 1842. "Bichat designates the heart, the lungs, and the brain, the 'trépied de la vie,' in some part of his celebrated work and considers sudden death as originating in one or other of these organs. . . . Many facts lead me to believe that the cases of sudden death arise chiefly from interruption of the coronary circulation." [1]

HISTORICAL

Huchard (1889) attributes the first observations on coronary sclerosis to Drelincourt (Boneti Sepulchretum, 1700), Thebesius (Disputatio de circulo sanguinis in corde) and Bellini (De morbis pectoris, Venice, 1703). But, as Riesman says (1922), "the most famous case is that of John Hunter, quite properly appreciated in its relation to angina pectoris by his friend and pupil, Edward Jenner. Parry, a country doctor, to whom Jenner communicated his observations in confidence, also in several instances diagnosed disease of the coronary arteries, and had the satisfaction of having his predictions verified at necropsy." Thrombosis of these vessels remained unrecognized until a later period, Cruveilhier (1850), according to Huchard, being the first to describe the condition.

Reports of rupture of the heart occur repeatedly in the older writings, perhaps because several famous men of medicine owed their death to this cause or to other coronary accident, notably Morgagni, Panum,

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1. No task could be more alluring than that of writing on angina pectoris, the "meditatio mortis" of Seneca, the awe-inspiring theme of Morgagni, Rougnon and Heberden, the nemesis of kings and wise men (but also of peasants). Someone else, however, will have to review that subject. Angina pectoris is a symptom, resulting from: disease of the coronaries, according to Mackenzie; aortic lesions if we believe Allbutt and Wenckebach; more reasonably, as the great Joseph Hodgson (1815) expressed it, "a train of symptoms accompanying almost all organic diseases of the heart"; but probably arising in certain cases, as Laennec has stated, "in persons who have no organic affection of the heart or great vessels." The pathogenesis is still undetermined. Eventually the known facts of cardiovascular pathology will be applied to the study of cardiovascular pain.

Hunter, Charcot, Nothnagel and William Pepper. Another fact which contributed to an early recognition of the condition is probably the occurrence in repeated instances among persons of rank. Thus the first case of heart rupture in the literature, according to Morgagni, is that recorded by Harvey of a nobleman who often suffered with paroxysms and oppressive pains of the chest. Finally,

> The disease growing more violent, he became cachectic and dropsical, and at length, being violently oppressed in one of the paroxysms, he died. In this patient, by reason of the circulation of the blood being obstructed from the left ventricle into the artery, the very substance of the left ventricle itself, which seemed to be pretty thick and strong, had been ruptured and perforated with a large opening, where it had discharged its blood; for the foramen was sufficiently large to admit a man's finger.

In the last of his series of ten collected cases of cardiac ruptures, Morgagni (1765) reports the rupture of the left ventricle found at the observation "made upon a most powerful monarch." Nicholls (1761) reports rupture of the right ventricle in another king, George II of England, who died while returning from stool. It is of interest that the latter case was associated with aortic aneurysm. Cardiac aneurysms, like ruptures, presented such a spectacular picture to the prosector of former times that they became easily recognized, though usually misinterpreted, as early as Morgagni's time. Infarcts, less distinctive and more variable in their appearance, were nevertheless observed and recorded under various terms, such as softening, fatty degeneration, etc. In most of the writings of the pre-Heberden period the condition of the coronary arteries is not mentioned. Nor is this the occasion for much wonder when we recall that in the majority of reports on heart rupture in the past decade, these arteries escape comment. Indeed, if we analyze closely the early writings on coronary disease, we must realize, even to the point of admiration, that in some of them our recent views find a fairly exact counterpart.

Bellini, 1703, is perhaps entitled to credit for first signalizing the association of coronary and myocardial disease. Huchard (1889) in his abstracts of 123 cases of angina pectoris with coronary lesions, relates that this Venetian observer found stones which had developed in the coronary arteries in a patient who died in a condition similar to that of angina pectoris.

"Mr. Hunter, and subsequently Drs. Jenner and Parry, ascribed the symptoms of angina pectoris to the deposition of calcareous matter in the coronary arteries of the heart," according to Hodgson (1815), who says further: "that a degeneration and wasting of the muscular structure of the heart attends an extensive deposition of calcareous matter in the coronary arteries has been noticed by Jenner, Parry, and Baillie." Hodgson himself cites three cases, one of them a sudden death, necropsy disclosing calcification of the single coronary arterial trunk, with result-

ing softening of the myocardium of the ventricles such that the finger could be thrust through any part of them. This sounds like a description of infarction.

A little later the infarct reappears with a different name. In Dublin, Robert Adams (1827) describes the heart from an anginal subject as "large, flabby, and of a yellow colour from fatty deposition," and records complete calcareous obliteration of the lumen of the coronary arteries. Other members of the Dublin school, including Cheyne (1818), Townsend (1832), Smith (1836), Stokes (1855), Bellingham (1849) and Kennedy (1849), designate myocardial necroses as fatty degenerations of the myocardium, sometimes connecting them with coronary sclerosis. Williams, London (1840), says:

> A pale, yellowish appearance of the substance of the heart is not at all an uncommon accompaniment of other lesions of the organ, especially adhesions of the pericardium and accumulations of fat; but I should be inclined to refer this to an altered state of the nutrition of the organ, owing perhaps to partial obstruction in the coronary vessels, rather than to the immediate influence of inflammation.

An ample summary of the results of these and other authors is given by their English contemporary Richard Quain (1850), the best known exponent of fatty degeneration as the end-result of coronary occlusion, who corroborates their view notwithstanding the wise admonition of Laennec—whom he cites—to the effect that these pale softened areas do not grease paper and that they owe their origin to "cachexia of the system."

The French workers in general refused to interpret such myocardial necroses as fatty in nature. The first of these is Laennec, quoted by Bertin, who distinguishes deeply colored and pale yellowish areas of softening, comparing the color of the latter to that of dead leaves. Bertin (1824) describes these in detail and ascribes them to carditis. Corvisart, 1812, first physician to Napoleon, disclaims having observed fatty degeneration of the heart; and Cruveilhier, in his atlas (1829-1842), exhibits lifelike colored reproductions of infarcts of the ventricle, which he says, however, are not comparable to fatty metamorphoses. None of these French authors attributes the process to arterial occlusion.

It is in a sense regrettable that Rokitansky, with his unparalleled necropsy experience, missed the opportunity of studying the coronary arteries, as did also Friedreich. Both believed fatty degeneration of the heart to be the most frequent cause of heart rupture.

From the foregoing it is apparent that various authors in England, France and the Germanic countries witnessed myocardial infarcts, with and without rupture, but missed their true significance—in some instances designating infarcts as fatty degeneration due to coronary anemia, in other cases failing to observe the coronary changes. It must be

accredited to the British writers that many of them emphasized the rôle of coronary obstruction in what they termed "fatty degeneration," and thus contributed to the final development of thought along the lines of myocardial disease.

Had Quain and other proponents of fatty change recognized, as did Dr. Hilton Fagge (1874), "that this affection never attacks the whole heart at once, nor even the whole of a single chamber," it is probable that the concept of infarction would have presented itself to the mind at once. It is evident that Quain and others of the authors cited were in reality describing anemic infarcts under the term "fatty degeneration."

The writings of Quain and others have established the idea of the common occurrence of a dense diffuse fatty myocardial degeneration so firmly in the traditions of medical teaching that it is difficult to supplant it. Thus the only death from spontaneous heart rupture reported in the Union Army during the Civil War was reported at necropsy to be due to fatty change, and Quain was cited as authority (Ingram).

As will be described later in this article, the pathology of cardiac infarcts includes fatty degeneration as an incidental and transient change, merely one of the transitions through which infarcted tissue passes in dying. Indeed, Master (1922) concludes as the result of his study of normal and pathologic hearts that the diagnosis of fatty heart is made too often. There are no symptoms peculiar to it, nor is there any pathognomonic sign for its diagnosis. Microscopically visible fat in human cardiac muscle does not prove degeneration, as fat droplets are normally present there.

Leyden (1884) disagrees with the majority of writers as to the commoness of this degeneration, and asserts that he saw traces of it but once.

CORONARY THROMBOSIS AND MYOCARDIAL INFARCTION

In reviewing the literature on coronary disease a sharp distinction must be drawn between the slow narrowing of sclerosis and the sudden occlusion caused by thrombosis and especially embolism. Then, as knowledge along these lines accumulates, it develops that a combination of these processes obtains. The early reports on sclerosis of the coronary arteries have been summarized briefly. Most of these. however, take no account of sudden occlusions.

The first author to report coronary thrombosis, according to Huchard, is Cruveilhier (1850), who perhaps describes an infarct without so naming it. The earliest direct reference in the literature, however, definitely affirming a relation between coronary thrombosis and infarction comes from Sweden, where Malmsten (1861), reports rupture of the left ventricle. "Microscopically the muscle fibers were here destroyed and replaced by a highly granular detritus, mingled here and there with fatty granules. In places there were small areas, visible even to the

naked eye, where only connective tissue remained, buried in the degenerated mass." The anterior branch of the left coronary artery contained an old white thrombus situated just before the entrance of the artery into the degenerated area. "The clot in the coronary artery was undoubtedly old. The arterial obstruction had resulted in a slow softening of the muscular tissue. Finally rupture appears to have occurred slowly." It seems only fair to regard the foregoing as a valid presentation of the concept of infarction. Malmsten, had he been imbued with the more modern ideas of publicity, might have devised names and built up a plausible schema, and thus immortalized himself. There is no question that by more diligently propounding what he did actually produce and establish, he might have occupied Weigert's pedestal.

An obscure American physician, Winsor, apparently shared Malmsten's disdain for greatness (or else was oblivious to the magnitude of his achievement, and therefore, as Blackstone might have expressed it in legal terms, slumbered on his rights), for in 1880, in describing a case of angina pectoris with rupture, he says: "In the vicinity of the rent—the characteristic appearance of the muscle was lost, the muscular fibres being here filled with a granular material, and in many places with minute fat drops." The walls of the left coronary artery were thickened and sclerotic and their lining covered with yellowish-white patches.

> At one point, about 3 cm. from the origin of the artery, one of these patches had so far protruded into the lumen of the vessel as to cause a coagulation of blood at that point, which coagulation had become adherent to the walls, thereby preventing the flow of blood through the vessel. The portion of the heart in which the rupture had occurred and in which the fibers were found degenerated corresponded to the territory supplied by the branches of this artery.

To Weigert (1880) is universally awarded the honor of being the expounder of the doctrine of cardiac infarction. In the course of a long dissertation on coagulation in tissues he makes the brief and seemingly casual remarks on cardiac infarcts which still constitute the genesis of this subject:

> With atheromatous changes of the coronary arteries thrombotic or embolic occlusions of their branches not infrequently occur. If the closures result slowly, or, more important still, in such a way that collateral channels, even though insufficient for nourishment, exist, there ensues a slower atrophy with disappearance of the muscle fibers, but without injury to the connective tissue. These destroyed muscle fibers are then replaced by fibrous tissue, and the so-called chronic myocarditis is nothing else but such a process.
>
> If, however, a very sudden complete cutting off of the blood supply occurs in certain parts of the heart, yellow dry masses entirely similar to coagulated fibrin result. Here also, however, microscopic examination reveals almost no fibrous exudate, but often an apparently quite normal tissue (even the cross-striations of the muscle fibers often recognizable) but all muscle fibers and all connective tissue are devoid of nuclei. A reactive infiltration of round cells and spindle cells is present in the vicinity.

Weigert definitely establishes the complete analogy between coronary infarction and the same process in other organs.

This epochal pronouncement was soon followed by corroborative reports from his colleagues in the Leipzig Pathological Institute, Cohnheim and Huber. Cohnheim (1881), besides his celebrated animal experiments, establishes coronary disease as the cause of infarction, myofibrosis and aneurysm. Huber (1882), in a study of eighteen cases of coronary sclerosis, points to the relation of thrombosis or embolism; infarction, myofibrosis and aneurysm; parietal thrombus; and heart rupture; and establishes the corollary that the secondary changes at the periphery of an infarct are the product of a nonpurulent inflammation having as its cause the disintegration of tissue elements. He also makes the important observation that left ventricular hypertrophy, when present, is due to other causes, i. e., general arteriosclerosis or kidney disease. "It bears no relation to myocardial and coronary disease, as was formerly believed, but always precedes these and is therefore older."

In 1880, Ziegler introduces the term myomalacia cordis, but his definition is not as convincing as the descriptions Weigert and Winsor published the same year. In his Lehrbuch (1887), however, Ziegler later gives a description of the types and results of coronary obstruction which, with minor changes, would be adequate in a present day textbook. It is to be noted that, in distinction to Huber, he correctly makes myomalacia cordis, not aneurysm, the direct precursor of rupture. He also amends Weigert's teaching—that all scarring of the heart results from anemic necrosis of muscle—with the wise reservation that a part of it is due to inflammation.

The interrelation of coronary thrombosis and myocardial ischionecrosis is further supported by the writings of Samuelson (1881), Birch-Hirschfeld (1883) and von Leyden (1884), in Germany; Popoff (1882), in Russia (see Odriozola); Duplaix (1883), in France (see Odriozola); and in England by Steven (1887), who mentions other lesser contributions of that time. Several creditable writings of that period must necessarily escape mention here because of lack of space. A myriad of pathologic and clinical reports have since appeared, and still continue to bulge the medical literature. Many of them neglect the principles established by Weigert and the other masters, while the great majority add at least to the statistics. But the fact is clear that the establishment of the great principles enunciated by Weigert was fulfilled decades ago when the classical theses of Odriozola (1888) and René Marie (1896) summed up and weighed the evidence of the masters, and gave to clinical medicine a working basis for the study of the great myocardial group of affections.

THE INCIDENCE OF CORONARY OBSTRUCTION

Before the time of Heberden and Parry, coronary disease scarcely finds mention in medical writings. It is inferred by Allbutt (1915) and others that in olden times sudden and painful deaths were often attributed to poison. Ramond and his associates (1921) suggest the suspicion of poisoning in a case of heart rupture, and Christian (1925) mentions the frequency with which sudden coronary deaths in notables are still reported in the daily press as due to acute indigestion or food poisoning. Those who are performing numerous coroner's necropsies find that in most of the suspected poisonings there is a fatal pathologic condition of the heart. Vital statistics without necropsy confirmation have no value, and even the necropsy is subject to error.

It is therefore not surprising that figures vary in different locations and especially in different necropsy services. Coronary death is a rare observation in the private hospital but a common one on the postmortem table of the coroner's morgue. Thus, if we take cardiac rupture as a criterion, there being no dispute about its identity, Krumbhaar's (1925) figure of seven such cases in 16,000 necropsies at the Philadelphia General Hospital; the Munich report of seven in 13,000 cited by Georg Meyer; the Leipzig series of nine in 8,000 (Krumbhaar), will serve to illustrate the rarity of this diagnosis in hospital practice. Most rupture cases terminate suddenly, and in some cities the majority of them reach the coroner's necropsy table. In contrast with the figures given above, Benson and Hunter report fourteen spontaneous ruptures of the left ventricle in 1,750 necropsies, probably the greatest incidence in any extensive series in medical literature. Krumbhaar and Crowell have collected 632 ruptures from the literature and add twenty-two hitherto unreported. This total of 654 certainly appears to be but an infinitesimal fraction of the actual total when we reflect that Portland, Ore., alone has had fourteen known cases within seven years, over one-fiftieth of Krumbhaar's total.

In view of the paucity of reliable data on rupture, it is obviously futile to attempt even an estimate of the frequency of cardiac infarcts and aneurysms, the statistics on these being less reliable. All writers agree, however, that both are considerably more common than rupture. Elliott (1924) cites Lucke and Rea's figure of fifteen aneurysms among 12,000 necropsies at the Philadelphia General Hospital, and in contrast refers to the figures of Le Count (1918), who in 175 necropsies in cases of cardiac death diagnosed fibrous myocarditis thirty-four times (with five parietal aneurysms) and acute coronary obstruction twenty-six times. Elliott says: "To reconcile such wide variation as exists between these two reports, perhaps some difference in definition of cardiac aneurysm should be taken into account. In 1908, McElroy could

find reported in medical literature but 300 cases of cardiac aneurysm." Le Count's figures are undoubtedly conservative. Benson and Hunter (1925), in 1,750 necropsies, largely in the coroner's service, encountered forty-six recent infarcts, eleven definitely circumscribed healed infarcts and nineteen cardiac aneurysms; total, after deduction for four duplications because of coexistence of old and recent processes, seventy-two infarcts and aneurysms. These data were nearly all carefully checked by microscopic study of the heart, including the occlusion of arteries. The only conclusion that can be reached is that coronary artery pathology is manifoldly more common than statistics indicate. More extensive and careful data are needed. The hospital figures are generally fairly adequate, but it is hoped that more statistics will be obtained from coroner's necropsy clinics operated in connection with accredited medical schools, especially in cities where (as in Portland) the coroner requires that sudden unattended deaths shall be diagnosed at necropsy.

It is to be suspected that in frequent instances an inexperienced operator at necropsy, unfamiliar with the delicate color changes in a fresh infarct, misses the diagnosis and fails to examine properly the coronary arteries. The author has for some years employed the coronal section method with a knife, recommended by Brault [2] and René Marie as early as 1896, and recommends formalin fixation of the heart before the cross-sectioning is done. Scissors are unsafe instruments for opening coronary arteries. Marie was uniformly successful in finding the arterial occlusion in his cases of infarct, and when others contrasted their lower figures with his, he asked "How has the examination been performed? Has one not forced the clot out?"

ANATOMY OF THE CORONARY CIRCULATION

On the subject of the anatomy of the coronary arteries little need be said. Two creditable monographs have appeared, The Blood Supply to the Heart, by Gross, 1921, and Die Arterien der Herzwand, by Spalteholz, Leipzig, 1924, and each has reviewed experimental results so fully that it would be useless to attempt any résumé at this time. The reader is referred to the extensive bibliographies in these works.

The purpose of these experimental investigations has been to determine the sources of the blood supply to the heart; the extent to which these anastomose, and the effect of closure of these vessels. The methods employed have been: examination of human and animal hearts by dissection, corrosion and clearing methods and by roentgenoscopy; experimental closure of coronary vessels in the living animal heart, and perfusion experiments to determine the rate of flow through each artery and their connections under varying conditions.

2. Mentioned by Ramond, Baudouin, and Bertrand, 1922, but place and date not given.

It can be stated without going into detail that most of the heart's nutrition comes from the coronary arteries, a smaller amount from the Thebesian vessels and a little from the connections of the coronary arteries with vessels outside the heart. The coronary arteries are only relatively end-arteries; anastomoses are present in varying degrees. The degree of anastomoses varies in hearts which are free from disease and the extent of anastomosis is increased through greater demands thrown on these vessels. Slow closure, as by arteriosclerosis, results in the development of collateral channels—even a rich network of anastomoses in extreme cases.

The result of sudden closure may vary in its morbidity in the normal heart, but in such a heart the arteries are usually almost end-arteries, and the effect of closure tends to be serious. Sudden death may occur, or infarction, or rarely no serious harm. In diseased arteries in which there has been a slow narrowing by sclerosis the harm resulting from closure tends to be per se of less consequence. With these few words I shall be compelled to leave this subject except so far as I shall have occasion to refer to special applications of it.

PATHOLOGIC ANATOMY OF CARDIAC INFARCTION

In 1884, von Leyden, in classifying cardiac injury from coronary obstruction, distinguished four groups (see Odriozola):

1. No myocardial change, death occurring so suddenly that time is not allowed for anatomic changes.
2. Myomalacia cordis (infarction).
3. Slower progressive closure of artery producing myofibrosis, either in disseminated islands, or in large confluent areas of fibrosis, or in the form of aneurysm.
4. Mixtures of these.

We may still accept Zeigler's definition of myomalacia cordis, or cardiac infarction, as "a softening of the heart muscle which follows arterial anemia. The main causes of this anemia are sclerosis, atheroma, calcification, and thrombosis of the coronary arteries and their branches, less often embolic occlusion." The conditions for infarction imply further, however, that the artery must be an end-artery, or terminal artery, i. e., one without sufficient anastomoses to take care of nutrition. In the case of the heart, the infarct is usually smaller than the area formerly supplied by the occluded artery, as some slight collateral circulation is usually present, either in the form of anastomosing twigs or of branches from another source mingling or dovetailing with those of the artery which is occluded.

In this connection, Oberhelman and Le Count's anatomic studies, 1924, are fundamental, and establish definitely by injection that human

hearts vary physiologically and pathologically in their degree of anastomosis. They classify their twenty-six hearts studied as follows: In nine healthy hearts without noteworthy arterial disease the coronary arteries did not anastomose appreciably; in five other apparently equally healthy hearts without arterial disease anastomoses were present to a considerable degree; in a third group of four hearts without myocardial change, but with narrowed arteries, free anastomosis was present; and in the fourth group of eight hearts with extensive myocardial change and narrowing or occlusion of one or more arteries abundant circulation was present.

From these results it appears that in some normal human hearts, the coronary arteries may be end-arteries, and it is in this type that sudden occlusion of an artery probably results in prompt death. In other normal hearts with considerable collateral coronary circulation, sudden occlusion of one of these vessels may be well tolerated, or perhaps result in infarction, while in the last two groups, with slowly developing sclerotic narrowing of the coronary arteries, allowing time for the development of collateral channels, coronary occlusion is usually better tolerated. It must be concluded, then, that arteriosclerotic narrowing of the coronary arteries, as related to thrombosis of these vessels, is not an unmitigated evil, in that it gradually prepares them for the catastrophe that is to come. Silverthorn (1898) and Allbutt (1915) also reach the conclusion from a clinical standpoint that in thrombosis the rate of closure of the artery is important. Of interest in this connection is the observation of Kretz (1925) relating the thrombosis of both coronary arteries without marked disturbance. This observer believes that the heart muscle may receive part of its supply direct from the ventricles. Indeed, Crainicianu (1922) holds that the Thebesian vessels play a much more important rôle than the coronary sinus.

Ziegler's description of infarction (1887) may be accepted as classical:

> The appearance of the softened areas varies according to their age and blood content. Shortly after the beginning of the anemia they are firm, and manifest themselves only by a dull yellow coloration of the heart muscle. After some time they become soft and friable and maintain a yellowish-white coloring; sometimes the cut surface sinks in somewhat, as the tissue is already softened. If the obliteration and occlusion of the arteries are followed by escape of blood from the capillaries, i. e., by hemorrhagic infarct formation, then the areas are from the beginning either dark red, or dark red with brown and yellow patches, or red in the periphery and yellow in the center. After some time they become grayish-yellow or grayish-brown or perhaps of a rusty color. Both anemic and hemorrhagic areas later acquire a gray transparent appearance, and retract somewhat below the level of the surface made by sectioning.
>
> The areas of softening form mostly in the left ventricle, particularly the apical portion of the front or back wall. They are sometimes found in other locations,

as in the wall of the right ventricle or rarely in an auricle. The papillary muscles are also occasionally the seat of the softening, indeed under certain conditions a whole papillary muscle may be converted into a brittle yellow or a hemorrhagic infiltrated tissue. If the softening extends to the intima, thrombi develop on the involved areas in the form of heart polyps.

If the area of softening is extensive and reaches entirely or nearly through the whole muscularis, rupture of the heart wall occurs.

The tissue changes are partly regressive, partly progressive. The anemia produces destruction of numerous muscle cells, and accordingly in the yellow-appearing areas are muscle fibers in various stages of disintegration. Clouding or homogeneous degeneration occurs, with fragmentation and finally the transition to granular detritus. In small areas of softening the process may end with the obstruction of the muscle cells, but in other cases the connective tissue also suffers changes, so that their nuclei in places no longer stain and granules are deposited on the pale fibrils. In cases of hemorrhage red corpuscles in their normal state or in various stages of disintegration may be present, or only pigment granules may remain. In rupture of the heart wall the site of rupture is infiltrated with blood.

When a certain stage is reached, the reparatory process starts. The detritus is absorbed, and repair by cicatrix formation occurs. In the meantime round cells wander out of the vessels, and a reactive inflammation occurs. The detritus is phagocyted or dissolved and absorbed, and vascular granulation tissue and connective tissue form. Thus the necrotic area becomes replaced by scar tissue. These scars may be reddish-gray or transparent gray, but become firm and white as they lose their cellular elements. If the scarred area is extensive the pressure of the blood may produce an outpouching of the wall—the partial heart aneurysm.

Others, including René Marie (1896), have given good descriptions.

The pathology of infarcts in experimental animals is equally instructive. Cohnheim and von Schulthess-Rechberg, 1881, observe that, when an arterial branch is occluded, the area of heart muscle supplied by it becomes first pale, then of a livid bluish color. Kolster, 1893, reports the appearance of experimental infarcts of various ages. This and other references on the subject are cited by Karsner and Dewyer (1916), who have conducted an extensive study of thirteen infarcted dog hearts. They conclude that:

Ligation of the coronary artery of the dog leads to the formation of a focalized area of congestion, hemorrhage, edema, cloudy swelling, fatty degeneration, granular and hyaline necrosis of the muscle, and supporting tissue. An infarct is produced which fundamentally has the same characters as infarcts of the kidney, spleen and lung. The infarct of the myocardium is at first hemorrhagic and later undergoes decolorization and cicatrization. The removal of the necrotic material is accomplished by liquefaction and the action of polymorphonuclear leukocytes, fibroblasts, polyblasts, and multinucleated giant cells. The results do not indicate that true regeneration of muscle occurs.

CHANGES IN THE CORONARY ARTERIES

The obstruction of arteries may be a slow one from sclerotic closure of coronary orifices, atheroma, atherosclerosis, syphilitic arteritis, various chronic endarteritides; from pressure from without, notably in encase-

ment by myocardial or other scars and in encroachment of dissecting aneurysms. Sudden obstruction is due to thrombosis, less often embolism; rarely dissecting coronary aneurysm; acute arteritis and endarteritis, and as reported by Herrick (1912) and Smith (1923) has been caused by surgical tying-off of a coronary artery. The most common of all is a mixed type, the chronic narrowing complicated by sudden thrombosis or even embolism. Besides the causes of coronary obstruction enumerated, some closely related lesions of these arteries, such as aneurysm and rupture must be discussed in their place.

Thrombosis.—Thrombosis was diagnosed by Hammer (1878) before Weigert's description of cardiac infarction. As Longcope (1922) and Libman (1925) have maintained, it can occur with or without accompanying or preceding sclerotic changes of the vessel wall. Medical writing contains several references, and could contain more, of thrombosis arising suddenly in vessels which are not sclerotic. Sometimes diabetes or other constitutional disease is attended by sudden thrombosis of the coronary—as of other—arteries. The conditions for thrombosis in a general sense, constitute too large a subject for consideration here, and form material in themselves for an extensive review.

Benda (1924) makes an observation on thrombosis of veins which applies equally to arteries: that thrombosis is a pathologic change of veins, but even more of their contents, the blood. In our whole consideration we must keep before our minds this important principle which is neglected in most writings on coronary disease. Thrombosis of these vessels is due, not entirely to changes in the vessel walls, but also, and perhaps equally, to changes in the chemical constitution of the blood, the chemicophysical properties such as viscosity, and likewise the lowered tension which is almost universal in these cases. It would seem worth while to work out the chemistry of the blood and other functional tests in selected cases of coronary pathology. Libman (1919) raises the question: What is the factor which determines the development of thrombosis in an arteriosclerotic vessel? But this question is chiefly unsolved.

Most of the cases of coronary thrombosis in the more accurate reports are properly described as occurring in arteries already narrowed by arteriosclerosis or atheroma or calcification. René Marie (1896) describes the histology of the occluded arteries in some detail, but somewhat confuses atheroma, endarteritis and thrombosis. It is evident in many of the descriptions and also from the author's personal study of numerous sections of occluded arteries that the intima is roughened, in many instances broken in a physical sense, permitting operation of the physiologic laws for the liberation of tissue elements as applied to coagulation. Such breaks in the integrity of the intima sometimes permit the escape of blood between or into the coats of the artery, forming the

dissecting hemorrhage or dissecting arterial aneurysm mentioned by Le Count (1918) and others. These may induce occlusion by pressure or may lead to the terminal thrombosis within the lumen.

Thrombosis in the cases without previous sclerotic narrowing of the arteries is usually fatal, and probably accounts for most of the cases of sudden coronary death in the first attack, such as are commonly encountered by the pathologist in the coronor's morgue but never in the hospitals. The more protracted clinical cases, with anatomic infarction, even repeated, and with formation of aneurysm, are usually those of combined thrombosis and preceding sclerosis.

The histologic appearance of fresh and of healed coronary thrombi corresponds with that of similar thrombi in other tissues, yet deserves mention. The literature contains but scant references. If histologic examination of occluded vessels were made in all cases, our knowledge of the whole process might be enhanced and the statistical data would certainly be more reliable. In a large percentage of the reports on cardiac infarction, aneurysm, myofibrosis and rupture, the coronary arteries are stated to be "sclerotic" or "nearly occluded by atheroma" or the equivalent, and often no evidence of any histologic examination is presented.

In most instances of old healed infarcts and aneurysms and in many cases of myofibrosis the occluded artery has undergone repair. Within twenty-four hours after the occlusion, fibroblasts and endothelial buds can be seen invading the clot, and in a few days, before the erythrocytes have undergone complete disintegration, connective tissue has largely replaced the fibrin. Recanalizations, single or multiple, often develop, sometimes through the heart of the clot, at other times along the side of it, and the circulation is reestablished. In the meantime, collateral arterial channels have also formed, giving rise to such close meshed networks as are portrayed in the latter decade roentgenograms of Gross (1921) and of Le Count (1918). It is apparent that recanalizations form, not only in occluding thrombi, but in the granulations within the thickened sclerotic walls of certain arteries whose lumen is nearly or quite obliterated. The reader is referred to Jores (Henke and Lubarsch's "Handbuch," 1924). A type of recanalization is also thought by some authors to occur in syphilitic arteritis, as mentioned later.

Differentiation must be made microscopically of thrombosis, arteriosclerotic occlusion and arteritis and endarteritis—syphilitic and otherwise. Not until this is done can we say that an artery is or is not syphilitic.

The finding of coronary thrombosis without infarction in cases of sudden death without preceding symptoms is important. Little has been written on this phase of the subject, and no adequate data are at hand.

In general, only isolated instances have been recorded. Most of the cases must naturally occur in coronor's necropsy files. In the preliminary report on the Portland series, it appears that in fifty-four of 1,750 necropsies (mostly from sudden unforewarned deaths), there was fresh coronary thrombosis (verified microscopically) without infarction or aneurysm. Many, perhaps most of these, represent death in the first attack, before an anatomic infarct has had time to form.

Embolism.—Coronary embolism has always been considered rare and improbable because of the right-angled departure of these vessels from the aorta. René Marie, in 1896, admits only a single case, that of Virchow, as proved. A few are reported, however, from time to time, and are usually suddenly fatal unless small. As elsewhere, any insoluble foreign material, solid, liquid or gaseous, may form an embolus. Coronary embolism may, therefore, be classified as follows:

(*a*) Air embolism is incidental to a similar general process.

(*b*) Fat embolism is likewise incidental.

(*c*) Mycotic embolism arises in cases of pyemia, and is usually characterized by one or more small or large purulent infarcts. The author, like others, has observed several cases. In case of large infarcts, death may result from cardiac anemia or, according to Silverthorn (1898), from abscess with rupture; but more often it is caused by the accompanying acute myocarditis and general sepsis.

(*d*) Vegetations from heart valves were the source of coronary embolism in Huber's case (1882), Le Count's (1918), and perhaps Locke's case of rupture of the right ventricle (1925).

(*e*) Thrombi produced embolism in Virchow's case; in Chiari's (1897); in three cases collected by Gallavardin (1913), and in his own case of saturnism having a parietal thrombus of the left ventricle at the site of a cicatrized infarct; in the case described by Lamb (1913, with review of the literature); the case of Le Count (1918); one from Murray (1926); four from Wolff and White (1926), and several in the Oregon series. Oestreich, 1896, describes a remarkable case in a man aged 32 who died suddenly in bed in the early morning following his wedding. Necropsy disclosed early arteriosclerosis of the ascending aorta, with an attached pedunculated thrombus of the size of a cherry pit hanging over the mouth of the right coronary artery and closing it like a valve. A piece of this had lodged in the first portion of the left coronary artery, obstructing it also. Otherwise the coronary arteries were free from change with the exception of slight atheroma, and the heart was grossly unchanged. Microscopic examination disclosed what the author considers to be agonal fragmentation of the heart muscle fibers from ischemia. Benson and Hunter (1925) observed five instances of coronary thrombotic embolism without anatomic infarction in coroner's cases with sudden death and no preceding symptoms.

(*f*) Plaques or particles may be loosened off from atheromatous lesions of an artery and carried further along in the course of the artery to occlude it. Panum (1862) reported such a sudden death for Thorwaldsen in a Copenhagen theater. Among several reports Dock (1896) and Le Count (1918) describe a similar case each. Allbutt (1921) also discusses accidents of this kind in syphilitic arteries. There is reason to believe that this type of disease is commoner than usually supposed, but overlooked at necropsy.

Dissecting Aneurysms.—Dissecting aneurysms of the heart may arise at any point of weakening in the endocardial lining of the heart, but more often about the aortic cusps. They are probably represented to some extent in the older writings by the reported partial ruptures of the heart. It is possible that they sometimes result in rupture of the cardiac wall. I have one in my collection which, starting in the aorta, dissected the left ventricular wall, and ruptured here into the pericardial sac. Another, of aortic origin, dissected the atrial septum, and bulged into the left auricle as a large whitish, fibrous, thin-walled aneurysm. Grayston, 1906, reports total obliteration of the right coronary artery by the pressure of such an aneurysm, and Oberhelman (1922) reports a somewhat similar occurrence, though not conclusively proved. Dissecting aneurysms are made the subject of a detailed thesis with long bibliography by Vestberg (1897), who collected fifty-nine cases besides his own single one. He classifies them as parietal, septal, valvular and interparietal, the point of predilection being, however, at the junction of heart and aorta.

ARTERITIS AND ENDARTERITIS

Acute arteritis is an old subject in the literature, and its bibliography is extensive. Ophüls (1921), in his valuable résumé starting with the remarkable citation of Tufnell (1853) who found multiple acute arteritis complicating an endocarditis, has given the important references from early times up to 1921, and it is unnecessary to recount them here. Out of the numerous reports he admits only a few as typical, and enjoins caution in making positive assertions. Various septic infections, also acute rheumatic fever with its endocardial and other manifestations, account for most of the cases, and it is apparent that there have been authentic examples of acute arteritis secondary to rheumatism and pyogenic infections.

The affection of the artery was described as transitory and without closure in certain instances (Barie cited by Ophüls), but in our consideration we are concerned with three possible occluding effects of acute arteritis: acute inflammatory closure, which, though conceivable, does not seem to be definitely established in any case; resulting thrombosis of the artery (case of Krauss, 1899, cited by Jores, 1924), with infarct formation in the case of terminal arteries, as claimed by several authors cited by Ophüls; and the production of arteriosclerosis, as maintained by Queuille in his Paris thesis (1906) and others. Roche and Burnaud (1908 Ophüls), distinguish two types of arteritis, one with, the other without, arterial closure, infarction resulting in the former case.

Coming specifically to the heart, rheumatic arteritis has been extensively studied. Rheumatic periarteritis was reported by Romberg (1894) and Rabé (1902); endarteritis by Cowan (1903); both endar-

teritis and periarteritis by Coombs (1908); and involvement of the media as well by Klotz (1912), who mentions that even the larger arteries are damaged by the inflammatory process, which travels along the vasa vasorum.

Jores (1924) attributes these instances of acute arteritis, mostly from French authors, and especially experimental purulent arteritis, to degenerative and proliferative processes of early arteriosclerosis.

It is evident that more definite data must be obtained before we can hope to establish a connection between acute arteritis and coronary occlusion in any form. Further histologic study is required, as questionable instances have been reported of sudden thrombosis of the coronary arteries without previous changes in the vessel wall. Such occurrences, if closely studied, might possibly be explained on a histologic basis.

Several proliferative processes in the arterial wall with narrowing of the lumen are grouped under the term "productive endarteritis" by Jores, who emphasizes the difficulty of deciding in every case, even in the presence of round cell infiltration, whether the intimal thickening is of inflammatory origin or not. This change probably corresponds with what Friedlander, 1876, in smaller and medium-sized arteries calls endarteritis obliterans, including the narrowing of small arteries such as is found in interstitial inflammation, in phthisis and in regions with syphilitic and nonsyphilitic granulation tissue formation. Gradual obliteration of the lumen may occur.

Periarteritis Nodosa.—Periarteritis nodosa is also connected with our subject. According to Jores, who gives a full bibliography, it was observed by Rokitansky in 1852 and given detailed description and its present name by Kussmaul and Maier (1866). In all, fifty-two cases were collected up to 1920 by Klotz (1917), who reduces the number to forty-three by dropping the syphilitic cases, and then adds two cases of his own. This author attributes the indicated mortality of 100 per cent to failure of recognition in nonfatal cases. In spite of the superficial resemblance of the perivascular infiltration to that of syphilis, he rules out the latter because of the inability of himself and other writers to demonstrate spirochetes. He obtained various pyogenic organisms from different lesions, but especially types of streptococci, and was able to produce somewhat similar lesions in rabbits. With this may be compared Haun's reproduction of experimental vascular lesions in guinea-pigs by injection of unfiltered blood from a human case (Haun, 1920, cited by Harris and Friedrichs). Also Harris and Friedrichs, 1922, report that by injecting into rabbits the Berkefeld filtrate of ground-up human lesions they reproduced the disease in the animals, including "periarteritis and arteritis showing mural necrosis occasioning aneurysm formation, thrombosis and hemorrhagic extravasations with retrograde

changes in the organs." They discuss the etiology and morbid anatomy, and eliminate syphilis as a cause as do most authors; and discount any suggestive importance of positive Wassermann reactions obtained in certain cases. They fail to demonstrate *Spirochaeta pallida,* and also adduce the supportive evidence of similar lesions found in the stag by Lupke (1906) and in the pig and calf by Guldner (1915). Ophüls (1923) reports an example of periarteritis nodosa which probably brings the number to about seventy.

For detailed views on etiology, morbid anatomy and symptomatology, reference is made to the extensive bibliographies found in the reports already cited. We are concerned here with the following facts as given by Jores (1924). Periarteritis nodosa involves especially arteries of the general caliber of the coronaries. Aneurysmal dilatations are generally, though not always, present. Intimal thickening and thrombus formation are sometimes present, and infarct-like necroses have resulted in the heart and other organs. Mönckeberg (1924) also cites the circumscribed pale yellow areas of myocardial necrosis observed by Veszpremi and Jancso, and the subacute interstitial myocarditis with multiple cardiac infarcts, as reported by Hart. Mönckeberg emphasizes the contention that myocardial changes due to periarteritis nodosa explain certain instances of myofibrosis in the absence of complete coronary occlusions induced by atherosclerosis.

According to Ribbert (1897 cited by Mönckeberg), gradual atherosclerotic narrowing of the coronary arteries leads first to areas of fatty myocardial change, then to complete destruction of the muscle, the defects being filled in by fibrous tissue. These myofibroses must necessarily be difficult to distinguish from those due to productive endarteritis or to periarteritis nodosa, and will in many cases resemble the scarring caused by syphilis.

Letulle (1897 Mönckeberg) believed that hypertrophy causes a diffuse myofibrosis by two stages—one of muscular overnourishment and overgrowth, the other characterized by loss of muscle substance and hyperplasia of interstitial tissue. Mönckeberg also maintains that dilatation and hypertrophy, as stated by Stadler, go hand in hand, and that both are related to the development of diffuse muscular fibrosis. He also discusses the myocarditis with scarring which occurs in diphtheria, typhoid, influenza, and other inflammatory diseases, and cites Aschoff's occasional finding of focal interstitial myocarditis due to streptococcus.

RHEUMATIC DISEASE

Rheumatic disease concerns us especially in this connection because of the myocardial changes that must be differentiated histologically from those of coronary atherosclerosis and thrombosis and from those of

syphilis; also because of the frequent occurrence of pericarditis which much be distinguished from that of syphilis and of cardiac infarcation; and because of certain similarity between the arterial changes of rheumatic fever and those of syphilis and also of periarteritis nodosa.

The literature on rheumatic fever is extensive. The Aschoff bodies, which Mönckeberg (1924) says remind one of periarteritis nodosa, offer the best positive differentiation of the condition, but unfortunately are not constantly recognizable, or as Holst (1921) suggests, may be represented in certain instances by old healed traces of nodules. This author maintains that these specific lesions are present only in patients who have had preceding febrile rheumatism. Fahr (1921) mentions perivascular edema with mucoid connective tissue change, and even with necroses of the outer portion of the vessel wall. This change in the vessel wall amounts to a disappearance of areas of the wall tissue and replacement by a loose pale blue staining mucoid tissue. There may be hyaline thrombosis of numerous small arterial branches. Changes in the myocardium, according to Romberg (1891), may be nonspecific, with round cell infiltration, scattered large epithelioid cells like those in the Aschoff bodies, and with areas of myofibrosis; or, as in Takayasu's description (cited by Mönckeberg), the Aschoff bodies may identify the myocarditis as rheumatic.

The rheumatic changes in arteries have received detailed study in America. Klotz (1912) made important observations on the aorta in acute rheumatic fever, chronic recurrent cases of the same disease and cases of chronic rheumatism.

In the acute cases the nutrient vessels had encroached beyond the outer third of the media, and were surrounded by infiltrations of plasma cells and lymphocytes. In the vicinity of these vessels the elastic fibers were interrupted, often appearing as if broken, and the muscle elements had disappeared. In the adventitia also were diffuse and perivascular infiltrations of lymphocytes and plasma cells, with only a few polymorphonuclears, and endothelial proliferation and sometimes fibroblasts were observed.

In the recurrent and chronic cases, the vasa vasorum were often present in the middle third of the media, and were surrounded by a large amount of fibrous tissue. In the more chronic cases a nodular intimal fibrous thickening was found.

From these results Klotz concludes that he is dealing with a true inflammatory process centering about the smaller arteries. The disease bears a certain resemblance to syphilis, but with less pronounced lymphoid infiltration, less fibrous tissue growth. The capillaries do not invade the media as extensively as in syphilis, and the nodular thickening is not as extreme.

Pappenheimer and von Glahn, in an extensive histologic comparison of rheumatic and syphilitic aortas, find points of differentiation which are fairly constant. In their acute rheumatic aortitis (1926), both their description and plates show perivascular infiltrations of the vasa vasorum with small round cells, plasma cells, and polymorphonuclear leukocytes, a type of lesion differing from the Aschoff body, and requiring caution to avoid confusion with the perivascular infiltration in syphilis. In their earlier work (1924), these authors refer to flame-shaped scars about the nutrient vessels of the media and consider these the sequel of the acute rheumatic lesion mentioned. They describe in detail the diffuse changes in the media and adventitia, and the reader should consult the original, with its convincing histologic description and clear illustrations. More recently, von Glahn and Pappenheimer (1926) described the specific lesions of rheumatism in peripheral blood vessels. Syphilis and rheumatism of the heart and aorta require further differential study. The histology of streptococcus disease of the vascular system is also an almost untouched field (see results of Thalhimer and Rothschild, 1914). No attempt is made to review the subject in this presentation.

Compensatory thickening of the intima and other adaptation processes in blood vessels are considered at length by Jores, with extensive bibliography. Arrosion is described by the same author as another condition of vessels which may lead to obliteration of the lumen. It consists of an invasion of the vessel wall from without by suppurative, necrotic or malignant processes, which may penetrate to the intima, causing thrombosis or aneurysm or rupture. Tuberculosis, according to the author cited above, may gain access to the vessel wall in this way, or may start in the intima.

ATHEROSCLEROSIS

In considering atherosclerosis, we cannot better acquire a background than by reading such valuable summaries in our own tongue as Ophüls' "Arteriosclerosis and Cardiovascular Disease," 1925; and, in German, Jores, on arteries in Henke and Lubarsch's "Handbuch." It is not possible in a definite space of time to exhaust the latter author's twenty-five pages of bibliography alone on arteries, but if we even acquaint ourselves with the very complexity of the problem, we shall be guarded against concluding too hastily that coronary occlusion is caused always by arteriosclerosis, or, on the contrary, that syphilis is the usual cause of myocardial necrosis. The problem is by no means so simple.

The great weight of evidence still points to atherosclerosis as the most common cause of slow narrowing of the coronary, as of other arteries, therefore the most common factor leading to coronary thrombosis and infarction. It would be of prime importance, therefore, to determine the

underlying causes of arteriosclerosis. Ophüls, 1921, enumerates the various theories up to his time: that of inflammatory origin (Virchow), those of mechanical wear and tear, or toxic causation including epinephrine, and the feeding experiments initiated by Ignatovski and since carried on by various workers, using different diets, especially cholesterol-containing diet. Cholesterin feeding has undoubtedly produced certain lipoid deposits in the aorta; epinephrine has caused aortic sclerosis; bacterial cultures of different types have led to arteriosclerosis, and since the publication of Ophüls' review, Newburgh and Clarkson have reported successful results in rabbits by feeding diets rich in animal proteins. Still the problem is regarded as far from solved. Hereditary, occupational, psychic, endocrine, and other vague factors have been assigned. Ophüls' statistical study appears to point to acute septic diseases as a factor. The question has arisen in the minds of many whether some kind of chronic "brush discharge" of repeated anaphylactic shocks may not add a connecting link between the various factors which have been advanced. Bacterial products have been tried with varying success, and research must be directed further along the line of the effect of proteins and even of the cleavage products of protein. The author has in mind such suggestive results as reported by Longcope, 1915, on the effect of repeated injections of foreign protein on the heart muscle, and the results of Thalhimer and Rothschild, 1914.

RUPTURE OF THE HEART

As early as 1733, Morand observed softening of the myocardium. Blaud (Bibliothêque méd. t. 68, 1820, cited by Barth) in 1820 attributed rupture to a gelatinous senile degeneration; Rochoux (inaugural thesis, 1823), to softening of the heart.

Hodgson (1815) is entitled to the main credit for determining the pathogenesis of rupture. In a case of sudden death following cardiac pain he reported rupture of the left ventricle where "the degeneration of the structure of the ventricle had in one part proceeded to such an extent that the remaining fibres were unable to resist the force of the circulation." The left coronary artery was completely occluded by calcareous deposit. Elléaume, in his classical Paris thesis "Sur les ruptures du coeur," 1857, insisted on the interrelation of cardiac apoplexy, senile degeneration and anemia due to arterial change. He ascribed death in heart rupture to pressure of the extravasated blood.

The observation by Malmsten (1861) already mentioned is probably the earliest description of heart rupture in association with coronary thrombosis and both recent and cicatrized myomalacia. Barth (1871) was the first to establish definitely the principle that cardiac rupture is, in the great preponderance of cases, due to coronary occlusion. Ménard (1878) associated coronary thrombosis and cardiac rupture. Molliére

(1881), and especially Georg Meyer (1888), explained cardiac rupture in the modern sense. Other references to the old and recent literature can be found in the bibliography, but the reader is especially referred to the comprehensive study by Krumbhaar and Crowell (1925), who collected 632 cases of rupture from the literature and reported twenty-two previously unpublished; also the more recent article by de la Chappelle (1926). We shall merely add a few points to their extensive discussion.

Cardiac ruptures usually occur in the left ventricle, less often in the other chambers, at the site of recent infarction, or occasionally in old cicatrized areas with fresh necrosis. Other seats of rupture are: the papillary muscles, as in the cases of Corvisart (1812), Dennig (1909) (cited by Fischer), Wankel (1911, cited by Fischer), B. Fischer (1922) and Eichhorst (1921), the last being reported as due to syphilis; the interventricular septum, usually, though not always, in the pars membranacea (Markham, 1859; Tergami, 1876; Crowther, 1880; G. Meyer, 1888; Youmans, 1921; Faulkner, Marble and White, 1924; Martin and Waugh, 1925; Benson and Hunter, 1925) about twenty-five in the literature; and the valves, represented by Howard, 1925 (many more might be cited).

The coronary arteries themselves may rupture into the myocardium, or more often into the pericardial sac, as in Odriozola's five examples (1888), several of Virchow (1847), and those of Galliardi (1840), Rochester (1896), Dock (1896), Le Count (1918), Kalyanvala (1919), Kesteven and Verco (1920), Benson and Hunter (1925). Coronary aneurysm is reported by Odriozola, Le Count and others.

Other etiology for heart rupture than recent infarcation appears occasionally. Fatty degeneration has in general been abandoned, being at the best incidental and not etiologic. Certain legitimate references to this type of degeneration still appear, however, as in the cases of Aubertin (1924) and Warthin (1925), described later in this article, and are, according to the latter author, in many cases related to syphilis. Abscess no longer appears in the reports, as it probably referred in the old writings to soft infarcts. Cardiac aneurysm is occasionally reported as a cause, probably too frequently. Gummas with rupture were, according to Georg Meyer, first described by Oppolzer, but they also have disappeared from the literature as a cause. On the other hand, diffuse syphilitic myocarditis is occasionally blamed, probably in certain instances with truth, as in the three examples of Harlow Brooks (1921). Aubertin (1924), who gives a good summary of the pathology of rupture, cites exceptional instances of rupture without localizing lesions, but with chronic myocarditis or fatty degeneration of the myocardium. It would seem that such cases as these might well be stained for spirochetes (see also Warthin, 1918, 1925).

Authentic reports of rupture of tuberculous lesions are presented by Korybut-Daszkiewicz (1922) and Oudendal (1923). Tuberculosis of the myocardium is frequently reported. Of special interest are two reports by Swiss investigators, Massini (1921) and Lüscher (1921) on masked tuberculous myocarditis with animal verification.

Endocarditis appears frequently in the older writings as a cause of rupture, but is to be discounted. The more reliable recent reports include those of Claytor (1923), Locke (1925) and very few others. Claytor's appears to be in reality a dissecting aneurysm with rupture, judging by his description, and there is the possibility that Locke may have overlooked a small embolus. Endocarditis as a cause of rupture without embolism may be open to doubt even when a minute examination of the coronary arteries for embolism has been made.

Georg Meyer (1888) cites the only then known case of rupture of the heart due to echinococcus cysts, that of Dézeimeris (1834). Crowther (1880) describes a perforation of the interventricular septum by rupture of a hydatid cyst. Hynd (1924), in a case of sudden collapse and death with respiratory failure, finds that in the right ventricle a subendocardial cyst the size of a hen's egg has emptied its contents, consisting of smaller cysts, which prove microscopically to be echinococcal. Several cysts were present in branches of the pulmonary arteries.

N. D. C. Lewis (1925) gives the references on heart rupture in infancy and childhood, among psychopathic patients, and in mammals and birds.

It must be emphasized that cardiac rupture owes its origin, not, as Odriozola (1888) maintains in his Paris thesis, to slow arterial capillary ischemia and cardiac aneurysm, but as René Marie (1896), in his equally well-known Paris thesis has thoroughly established, to "a sudden and more or less massive ischemia due to the thrombosis of one of the branches of the coronaries. The myomalacia instead of slowly preparing the tissue for rupture is, on the contrary, sudden." This opinion is concurred in by Ziegler (1887) and by Robin and Nicolle (cited by René Marie). Cruveilhier in his celebrated works on anatomy in the first half of the last century and René Marie (1896) refer explicitly to two types of lesion as determining rupture, namely, the red areas and the yellow, the two often being combined to form a yellow area of necrosis surrounded by a red border of hemorrhage. Aubertin (1924) describes these hemorrhagic and anemic infarcts and also a third type, namely, rupture in the presence of occluding coronary thrombosis but without the presence of anatomic appearances of infarction. These are to be attributed to extremely recent infarctions in which the promptness of the rupture does not allow time for gross tissue changes. The possibility must be kept before us also of a rupture without infarct due to syphilitic myocarditis as emphasized by Warthin or to one of the less common causes already enumerated.

Reznikoff (1922) performed auscultation in one case at the time of rupture and describes the souffle due to blood pouring into the pericardial cavity. Rojas and Elizalde (1925) recite the references to delayed death in cardiac rupture.

PERICARDITIS IN CORONARY DISEASE

Pericardial exudation was observed in connection with myocardial degeneration by some of the earliest writers, and was even considered to be the primary cause of the myocardial injury (Rendu, 1887, cited by René Marie, Pawinski, 1897).

Bérard (1826) described pericarditis overlying an aneurysm of the heart, and correctly, though vaguely, ascribed its formation to the myocardial disease "just as localized pleurisies under the influence of tuberculosis of the lung." Ollivier (1834), in his seventeen collected examples of partial aneurysm, found adhesions of the pericardium in nine, and gave extensive references. Williams (1840), in London, associated pericarditis and myocardial degeneration, and even inclined to the belief that coronary obstruction might be concerned with the condition. Dehio's (1880) report of stenocardia following occlusion of the left coronary artery of the heart is an important contribution. Kernig (1892), in a study of angina pectoris, found at necropsy thromboses of coronary arteries, and he associates the pericardial symptoms in the days following anginal attacks with areas of softening which extend to the pericardium. Huchard (1899) also ascribed the pericarditis to coronary disease.

Sternberg (1910), in his scholarly presentation "Pericarditis Epistenocardica," with full bibliography, correlates the anatomic observations of Kernig with the clinical symptomatology, and distinguishes two types of cases:

(1) Recent closure of a coronary artery, infarct formation, acute pericarditis overlying it.

(2) Old coronary changes, scarring from myomalacia, pericardial adhesions over this.

(*a*) Scar small, superficial, unimportant.

(*b*) Scar large, usually constituting a partial aneurysm.

He believes that the healed pericarditis and the coronary sclerosis of John Hunter, who died an anginal death in 1793, belong in the second group.

Sternberg maintains that syphilis can produce pericarditis either by direct extension from the myocardium or by causing coronary arterial disease, and in this connection cites Mracek (1893), Rauscher (1902) and Stockmann (1904). On the other hand, he emphasizes that nephritis is a common cause of pericarditis, and must be ruled out. Various

clinicians, including Dock (1896), Herrick (1912), Gorham (1920), Pardee (1921), Longcope (1922), Blumer (1922), E. Smith (1922), Wearn (1923), Thayer (1923), Gordinier (1924), Rindfleisch (1924) and others have applied these principles to clinical medicine noting the type of pain and observing in varying incidence the prevalence of friction rub in the days immediately following the anginal seizure.

RELATED CARDIAC LESIONS

Partial or parietal aneurysm received its name and scientific classification from Bérard in 1826, but was recognized by Corvisart in 1812 and even by Morgagni in 1765. Breschet, in his well-known thesis "Anévrisme faux consécutiv du coeur (1827) collected and discussed ten cases. The pathogenesis of cardiac aneurysm has been explained by Cohnheim (1881), Ziegler (1887), Odriozola (1888), René Marie (1896) and many others on the basis of either slow arteriosclerotic narrowing of the coronary arteries with resulting disappearance of muscle fibers and replacement by scar tissue or, on the other hand, on the basis of the cicatrization of necroses resulting from coronary thrombosis. Aschoff and Tawara, 1906, found all transitions from fresh infarcts to scars. Many authors have since verified this view of myofibrosis by demonstration of the extreme arteriosclerotic narrowing of the coronary arteries or the finding of organized thrombi, often recanalized.

But Stevens sounds a note of conservation as early as 1887, when in discussing knowingly the types and causes of myocardial disease, he emphasizes the preponderating rôle of coronary obstruction, but cites cases which demonstrate that active inflammatory disease, such as rheumatism, may even in the absence of coronary narrowing result in fibrosis. Aschoff and Tawara (1906), and Coombs (1909) consider that some fibrosis may result in the myocardium from acute rheumatic fever, and Brooks (1911) finds myofibrosis in a high percentage of cases of endocarditis. Sternberg (1910) recognizes the rôle of coronary occlusions, but questions whether they explain all cases, and even maintains that syphilis is a factor, and cites references. Allbutt (1915) presents at considerable length the arguments against relating all cardiofibrosis to coronary disease. Space does not permit our reciting these, and the reader is referred to the original. Fahr (1921) considers the myocardial lesions in articular rheumatism and shows various stages from the perivascular nodes to fibrosis, and also compares the fibrosis in scarlet fever as being somewhat similar but capable of differentiation. Brooks (1921), in a series of 50 syphilitic necropsies from a total of 100, reports myocardial gummas in 5. In others he finds fibrosis either from low grade inflammatory hyperplasia or from healing of gummas or from nonspecific myomalacia resulting from endarteritis or thrombosis. Clawson

(1924) admits an occasional myofibrosis from rheumatism but affirms that syphilitic or other true chronic inflammation of the myocardium is rare.

Cohnheim establishes clearly the relation between coronory disease myocarditis and the accompanying aneurysmal dilatation. Aschoff and Tawara (1906) find all transitions from fresh infarcts to scars. Many authors have since verified this view of myofibrosis by demonstration of the extreme arteriosclerotic narrowing of the coronary arteries or the finding of organized thrombi, often recanalized.

Warthin, in his recent publication on syphilis (1926), describes aneurysms which he explains on the basis of an existing active syphilis corroborated by demonstration of spirochetes, but most authors have reported arteriosclerotic stenosis or organized thrombi of the coronaries in the majority of their cases, and the evidence, therefore, favors coronary arteriosclerosis and thrombosis as the most common but not sole cause.

Odriozola (1888) reports healed aneurysms possible but rare, and cites Rindfleisch. Such complete healing of aneurysms with later death from distinct causes is no longer considered rare but is represented in the more extensive series of coronary reports.

Parietal thrombus needs no extended discussion here. It is present in the ventricle as a frequent accompaniment of infarcts and especially of old infarcts and aneurysms. Corvisart (1812) observed apoplexy resulting from thrombus of the heart. That he understood the condition is evidenced by the fact that he quotes Albertini of Bologna on polypi to the effect that "the patients were attacked with vertigo, and sometimes with species of apoplexy."

Bérard (1826) recognized the overlying pericarditis and also the tampon thrombus on the endocardium as due to extension of the myocardial injury to the pericardium and endocardium, respectively. Ziegler (1887) described them in their full significance. Clinicians of later times have generally appreciated the connection between parietal thrombus and the resulting embolic involvement of various viscera, including the brain. A large percentage of apoplexy is recognized as originating in this accident. Multiple hemorrhagic infarcations in the lungs of these patients commonly lead to the false diagnosis of pneumonia—a mistake which, according to McNee (1925), is also made possible by the common occurrence of acute pulmonary edema.

There is little question that fibrous and possibly other types of endocarditis exist as an accompaniment of infarcts and myofibroses, but there appears to be no adequate differentiation in the literature between these and other types of fibrosis of the endocardium. Herrick, 1919, and others mention cases. Willius, 1919, gives an interesting classification according to cause, but his percentages may require further verification.

Other related pathologic conditions in coronary arterial disease concern the embolic phenomena and the effects of circulatory failure. These are fully discussed in most writings. Jaundice may be mentioned as a frequent symptom. Castex and Gonzalez in Argentina (1921) refer this symptom to defective hepatic circulation with impaired function, and suggest that it implies a fatal prognosis. Fishberg (1923) considers the subject from the standpoint of the bilirubin content of the blood, and confirms previous reports to the effect that bilirubin is increased in the blood in myocardial insufficiency. The yellow color in these cases therefore constitutes a true jaundice. This, with the usual cyanosis in extreme cases, gives the cyanotic icterus with its leaden or earthy hue referred to by Herrick, Libman, Paullin, Wearn, McNee and others, and occasionally confused with Addison's disease, carcinoma and other pigmentary affections.

Leukocytosis is usually present in infarction cases, ranging between 10,000 and 20,000, occasionally higher. This, together with a slight to severe febrile reaction usually present, and a frequent localization of pain and distress in the epigastrium, has on many occasions led to an erroneous diagnosis of surgical abdominal conditions. Suggestions of this type of clinical course are found in the literature from Corvisart's time and probably before; but to Herrick (1912) is due credit for having emphasized the resemblance of some of these cases to surgical conditions of the abdomen and for having outlined the criteria of differentiation between the two. Special interest has attached to confusion between coronary thrombosis and cholecystitis which has led to many blunders. Indeed, as McKeen (1926) says, coronary thrombosis may be accompanied by cholecystitis or cholelithiasis. Morgagni (1765) "assisted in the dissection by the celebrated Santorini" observed rupture of the heart in association with fourteen calculi in the gallbladder. Samuelson (1881) recites a case with coincidence, confirmed at necropsy, of gallstone colic and anginoid symptoms due to coronary occlusion. Many such reports might be cited. In the minds of some the suspicion has recently arisen that gallbladder disease is in some way related to coronary occlusion (Mayo, 1924). Willius (1924) states that "in eighty-six necropsies made at the Mayo Clinic in which sclerosis of the coronary arteries was found the gallbladder was diseased in 24 per cent." This raises the question of the criterion of gallbladder disease. Other reports have appeared which bear on this phase of the subject, but further study is required.

Special attention is invited to Obrastzow and Straschesko's (1910) valuable contribution in which they refer to the status gastralgicus; Osler's and Herrick's scholarly presentations; Paullin (1918), Levine and Tranter (1918), Levine (1920, 1921), Hamburger (1920),

Gorham (1922), Lian and Pollet (1924, cardio-gastro-anginal state), Willius (1924), Robey (1925), Riesman (1925), and others whose names will be found in the bibliography.

CARDIAC SYPHILIS

The subject concerns the congenital and the acquired forms. While Virchow correctly divided cardiac syphilis into fibrous and gummatous, we can probably best classify it as concerns this treatise into that of: (*a*) the aorta and aortic valves; (*b*) the coronary arteries; (*c*) the heart wall proper.

Syphilis of the aorta offers no difficulty in recognition in advanced cases. According to Jores (1924), Doehle, in 1885, described the wrinkled appearance of the aortic lining, and already in 1877 Laveran had ascribed the round cell infiltration of the media to syphilis. The gross and microscopic pathology is fully discussed in every textbook on pathology, and reference might be made to Thorel, 1903, or to Jores' recent work already cited. J. C. Allbutt (1921) aptly quotes Professor Turnbull that syphilitic aortitis is "pearly in tint—rubbery in consistence, crenated in outline, pitted on the surface, and passes into scar; calcification if any being scarce." Less pronounced involvement of the aorta requires special differentiation from rheumatic disease, as emphasized by Klotz (1912), and Pappenheimer and von Glahn (1924). In fact, Jores, as recently as 1924, expresses some doubt as to the incidence of rheumatic aortitis, and maintains that "a productive aortitis of non-syphilitic origin scarcely ever occurs." He admits, however, that in cases of mild mesa-ortitis one may search for other causes.

One important effect of syphilitic aortitis besides its connection with aortic valve syphilis and aortic aneurysm is the not infrequent closure of the ostia of the coronary arteries due to intimal thickening. This phenomenon is mentioned in the earlier writings and is encountered frequently in most of the later series. Indeed, the statement is often made that this is the only way in which syphilis produces coronary occlusion, but such statements are merely an evidence of insufficient study of the coronaries in cardiovascular syphilis.

As a matter of fact, syphilitic involvement of the coronary arteries occurs as a frequent accompaniment of cardiovascular syphilis, and probably has as great an incidence as syphilis of the smaller and middle-sized arteries in other locations. The only difficulty is in recognizing it, and for statistical purposes, it becomes of the greatest importance in cases of coronary obstruction to determine definitely whether the pathology in the arteries is that of arteriosclerosis or of syphilis, or perhaps of one of the other less common types of arterial narrowing already discussed. In most of the reports such a clear differentiation is not evidenced.

As stated earlier, there are types of productive endarteritis in which it is impossible to state on the histologic appearance alone whether the thickening of the wall is due to syphilis or not, and in such cases the staining for *Spirocheata pallida* may be the only criterion available. But in a large percentage of syphilitic coronary arteries the pathology is conclusive. Grossly, Marchand (cited by Jores) has found similar arteries in the brain rigid, thickened, grayish-white translucent and often considerably narrowed. The later writings contain similar descriptions of syphilitic coronary arteries. The intimal lining is irregularly wrinkled and distorted, and the adventitia is thickened and adherent to the adjacent reticular tissue. Gummas are occasionally, though not usually, visible to the naked eye. Brook's cases with gummas are referred to elsewhere in this review.

Microscopically there are the well-known characters of syphilitic inflammation: lymphoid cell and plasma cell infiltration of the adventitia, especially about the blood vessels; and changes in the media which may belong to either of two general types representing either active or inactive syphilis. Naturally, mixtures of these types may occur. The active or earlier stage is characterized by abundant patchy infiltrations of small mononuclear cells in the media, with interruptions of the elastic and muscular elements. These areas extend deeply into the media, or may even penetrate it to reach the thickened intima. The perivascular and other infiltrations in the adventitia may in this type be abundant and dense and may resemble microscopic gummas, with few or many Langhans giant cells at their periphery. Occasionally one sees gumma-like necroses with giant cells in the media.

In the later or inactive stage the inflammatory infiltrations are a less prominent feature. The muscle and elastic tissue have largely disappeared, being replaced by fibrous tissue, which is in turn hyalinized. Vasa vasorum of considerable caliber are often present in the depths of the media, and their walls are in varying degrees thickened and hyaline. With all these changes goes an irregularity and distortion of the elements in the wall which gives a typical impression of syphilitic damage and repair. In many specimens, as noted by Nissl (1903) and Alzheimer (1904), in arteries of the brain (cited by Jores), a peculiar proliferation of the intima occurs, with the result that in the original lumen of the vessel several smaller lumina are formed. The author has repeatedly seen this change in coronary branches of medium caliber, but is unprepared to speak for or against its syphilitic origin. The German writers have in general discredited it.

In other instances, especially when lipoid deposits and calcium salts are abundant, the question arises whether the distortion of the wall and the round cell infiltrations may not result from arteriosclerosis. In some

cases with slight perivascular infiltrations in the adventitia, rheumatic vascular disease must be considered, particularly keeping in mind Klotz' and Pappenheimer and von Glahn's portrayals of rheumatic arterial lesions.

Much more experimentation is required before absolute figures can be obtained on the relative incidence of arteriosclerosis and syphilis—and perhaps rheumatic infection, periarteritis nodosa and the various types of productive arteritis—as causes of coronary occlusion. This much is evident, however, that the histology of the arteries is not sufficiently studied. The discrepancy in the figures of various authors is too great.

Brooks (1921) reports syphilitic coronary arteritis in a majority of his fifty consecutive cases of clinical syphilis. In several instances the walls of the vessels are studded with minute gummas; in some there is a diffuse endarteritis; in others a periarteritis, but usually panarteritis is present—in one case with aneurysmal dilatation. He states that areas of round cell infiltration about the terminal arborizations of the coronary arterioles are frequent with parenchymatous degeneration of the adjacent muscle tissue and active hyperplasia of the interstitium. He cites Adler (1898) as the first to demonstrate these changes.

It does not appear to be established firmly that syphilitic coronary arterial disease actually produces thrombosis and infarction. In the reports of Randolph (1915), Le Count (1918), Dock (1918), Miller (1922-1923), Kerr (1925), Werley (1925) and many others, the association of syphilis with coronary thrombosis is asserted, but generally without histologic proof. Darling and Clark (1915) describe syphilitic obliterative arteritis of the great branches of the aortic arch, sometimes with thrombosis, but this involves only the beginnings of these arteries in the aorta. Warthin (1925) observes coronary thrombosis in none of his eight cases, but finds "syphilitic obliteration" of the left anterior descending branch in one, evidently without thrombosis. Mönckeberg and Jores (1924) do not cite any cases of thrombosis under these circumstances, as far as I can find. Further search of the literature might disclose authentically reported examples, but this much is certain, that the condition appears rarely as an established fact. It is surprising that plenty of instances are not on record, for it seems logical that such a process must occur on occasion, even if only by arrosion, as recorded in the case of tuberculosis by Jores. Further work is needed on this question.

Myocardial Syphilis.—The subject may be divided into: (*a*) heart changes due to occlusion of a coronary ostium; (*b*) changes in myocardium due to gradual or sudden occlusion of coronary arteries by syphilis; and (*c*) active and fibrous types of syphilitic myocarditis.

Sudden occlusion of an ostium by thrombus or embolus, as reported by Oestreich, 1896, and others need only be mentioned here. Such accidents, like embolism at any point in a coronary artery, usually result in sudden death, with or without anatomic evidences of infarction.

Syphilitic occlusion, frequently reported (Le Count's four cases, Benson and Hunter's six instances, and many others), accounts for most of the closures of the coronary orifices. The effects on the myocardium are similar in general to those of other gradual constrictions of coronary arteries. Ischemia of the heart with nonspecific myofibrosis may or may not be accompanied by an independent active syphilitic involvement of the myocardium. It is of importance here that anastomosis with the other coronary artery has had time to develop, and that the course of the illness is usually chronic. Acute coronary accidents may, however, result in sudden death at any time.

Likewise the myocardial changes attending sudden or gradual syphilitic narrowing or closure of the coronary trunk or branches will not differ materially from the effects of other types of obstruction in these arteries. If the occlusion be sudden, as in one of Warthin's cases, 1925, infarction or sudden death without infarction may result. Myofibrosis is probably more frequent, and may be complicated by the picture of active syphilitic myocarditis.

The old reports on syphilitic myocarditis are mostly unreliable. Grenouiller in his Paris thesis, 1878, cites Morgagni, Senac, Lieutaud, Portal, Corvisart, Julia and other early reports of historical interest, and tabulates twenty-four cases from the literature of 1845-1875, including one from Virchow, 1858, who divides myocardial syphilis into fibrous and gummatous. Grenouiller follows nearly the same classification but mentions pericarditis as a secondary complication. Numerous early references might be cited, but the effort would be poorly repaid, as most of the articles written before the discovery of *Spirochaeta pallida* in 1903 admit of no definite verification, although a few describe the histology with surprising accuracy.

Thorel, 1903, presents references up to his time, and also gives utterance to the prevailing belief in the infrequency of cardiac syphilis. He admits the gumma, but concerning Virchow's other syphilitic type—the interstitial—he says:

> Syphilitic fibrous myocarditis and its symptoms present nothing characteristic. The proof of a specific fibrous myocarditis in any given case is absolutely impossible, and I consider it pure speculation and not science when one calls myofibrosis —of whatever grade—syphilitic, because it is encountered in an individual who is infected with syphilis.

This opinion still prevails with most clinicians. Clawson (1924), in nine cases of definite syphilitic aortitis, finds only three with myocardial

fibrosis, and ascribes two of these to ordinary coronary sclerosis. He says myocardial syphilis appears to be rare. Innumerable citations could be adduced which agree with this. There is a growing tendency, however, to consider syphilis of the myocardium as frequent in much the same degree as syphilitic aortitis.

Jores also maintains with Thorel that Virchow's interstitial or fibrous syphilis has no criterion of differentiation from other cardio-myofibroses, except in the case of congenital syphilis. Even in the presence of miliary tubercle or gumma formation with Langhans giant cells, the differentiation between tuberculosis and syphilis is difficult in the absence of demonstration of the specific organism. He therefore adopts Saltykow's term specific productive myocarditis to designate this group of chronic inflammations characterized by proliferation of the intermuscular connective tissue. The occurrence of such a specific productive myocarditis with giant cells is fairly frequent in the author's series, and presents difficulties that can be solved in some instances only by staining for the causative organism.

One factor which has contributed more than any other to the recognition of syphilitic myocarditis as a pathologic entity has been the study of congenital syphilis as it affects the heart. Hektoen, 1896, in reporting a case, cites the early literature, including the report of Mracek, who, in turn, reviews the literature and cites four cases of his own. Hektoen describes gummatous and interstitial syphilitic myocarditis, as does Le Count (1898) in his case. Warthin (1911), in a study based on twelve cases, mostly in infancy and childhood, a few in early adult life, concludes that gumma of the heart is rare in congenital syphilis, and that the characteristic observation is a diffuse or localized interstitial myocarditis in which *Spirochaeta pallida* can be demonstrated. The bibliography of this subject can be found in the articles of Hektoen and Warthin.

"The New Pathology of Syphilis," by Warthin, 1918, perhaps furnishes the best summary of this author's divergences from the old lines of syphilitic investigation. His incidence of 40 to 50 per cent syphilis in his necropsy series as compared with 6.5 per cent in Symmer's series, will serve to illustrate his opinion on the prevalence of the disease. He concludes that the discrepancy finds its solution in the different pathologic criteria employed.

Warthin insists in this, as in his other writings, that too much emphasis has been laid on the gumma, from Morgagni's time to the present, and that in fact visceral syphilis is represented "not by gummatous processes, but by specific inflammatory processes, eventually fibrosis, usually mild in character, but acquiring pathological importance because of their progressive character."

Based on demonstration of spirochetes in various viscera by the Levaditi method, he concludes that syphilis as a latent infection is much

commoner than generally supposed—perhaps as high as 30 per cent in this country. The further conclusions in this extremely interesting and important work are familiar to most of my readers, or can be read in the original.

The important phase as concerns the subject of this review is the application of Warthin's views on myocardial disease, particularly as presented in his recent contribution, 1925, based on a study of eight hearts from cases of sudden death. He ascribes the sudden death to an acute exacerbation of previously mild latent processes in the heart and aorta. The chief gross feature in the hearts is the irregular "patchy and streaked areas of pale yellowish, grayish-yellow or gray color, without hemorrhage or congestion, scattered throughout the myocardium," and which "may easily be mistaken for anemic infarcts."

> The microscopical features of the cardiac lesions were areas of old fibrosis (completely healed myocarditis); subacute infiltrations of lymphocytes and plasma cells between the muscle fibers, with angioblastic and fibroblastic proliferation and interstitial edema; more acute areas of interstitial edema with infiltration of lymphocytes, plasma cells, monocytes and a predominance of polymorphonuclears. Spirochetes were found, particularly in these more acute areas.

The author quoted above states that changes in the coronary arteries were slight, except in one instance of infarction due to syphilitic obliteration of the left anterior descending artery.

The observation of the specific organism in the patchy lesions having such a varied and apparently nonspecific appearance seems to justify Warthin's contention that this is the only decisive diagnostic point. Having seen many of his spirochete preparations, I am convinced of the finality of his staining method.

It is to be recalled, however, that infarction is noted in only one of the eight cases, and coronary thrombosis is reported in none. Warthin suggests that the patchy syphilitic infiltrations described by him "may easily be taken for anemic infarcts, and probably are in the usual pathological routine." It becomes then a matter of the utmost pathologic importance to decide, if possible, whether investigators are actually mistaking syphilitic necroses for anemic infarcts. It is of course possible that such a thing may happen.

It must be borne in mind, however, that the real criterion of infarction is the demonstration of the abrupt closure of an artery, and it is claimed by the better investigators that coronary thrombosis was present in all or nearly all of their infarction cases. Thus, Wearn (1923), reports a thrombus definitely located in eighteen of his nineteen infarcted hearts; Faulkner, Marble and White (1924) accounted for the occlusion in all of their thirty cases; Le Count (1918) also in his twenty-six, and we might recount other similar series. These were evidently infarction cases

due to coronary thrombosis or other known causes. It is equally evident that Warthin's were syphilitic cases without infarction.

One answer to this seeming conflict is perhaps that Warthin's series, collected over a period of twenty years, represents a totally different source which has excluded thrombosis cases. The ages of his subjects are significant—53, 42, about 55, 25, about 45, 44, 57, and 29; average about 44. This age incidence is in general lower than that usually encountered in series of infarction cases. So it is likely that, in part at least, Warthin in describing his syphilitic series and others in presenting their infarction series are discussing two distinct entities.

There is, to be sure, a serious discrepancy between the different figures on the incidence of syphilis. It is quite possible that most clinicians and many pathologists are overlooking some instances of latent cardiac syphilis by not rigidly carrying out the histologic study of the myocardium and coronary arteries; on the other hand, it is equally true that coronary thrombosis and infarction are found as the cause of the majority of spontaneous sudden deaths in the large coroner's necropsy services. Coronary thrombosis is established as the cause of immediate death when the occluded vessels are terminal arteries; infarction in hearts having some degree of coronary anastomosis; and little or no immediate damage in those which, prenatally or through disease, have acquired adequate collateral circulation. Myofibrosis from organization of ischemic necroses and from the ischemia due to slow sclerotic coronary constriction is also certain. The field which still requires considerable exploring is the great group of chronic inflammatory interstitial myocarditides, including those of syphilis, rheumatic fever, periarteritis nodosa, streptococcus and probably others still untouched.

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*Because of the size and broad scope of the bibliography, it was thought best to divide the references into the following groups: (1) coronary obstruction, (2) coronary anatomy and experimental coronary obstruction, (3) heart rupture, (4) rheumatic heart disease, (5) arteriosclerosis, arteritis, etc., (6) coronary disease with abdominal symptoms, (7) angina pectoris and (8) cardiac syphilis.

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Notes and News

University News, Promotions, Resignations, Appointments.—Dr. W. W. C. Topley, professor of bacteriology in the University of Manchester, has been appointed professor of bacteriology and immunology in the University of London.

Dr. Albert G. Nicholls, for about twelve years professor of pathology and bacteriology, Dalhousie University, Halifax, and pathologist to the Province of Nova Scotia and director of provincial public health laboratories, recently resigned these positions. Dr. Nicholls formerly was assistant professor of pathology at McGill University Faculty of Medicine, Montreal, under the late Professor John George Adami, with whom he cooperated in the authorship of books on pathology.

Dr. Aldo C. Massaglia, professor of bacteriology and pathology in the school of medicine in the University of Mississippi, died recently while en route to America from Italy where he had been visiting his father. Dr. Massaglia was professor of pathology in the university of North Dakota from 1921 to 1923.

Dr. Wilfred Watkins-Pichford, director of the South African Institute for Medical Research, Johannesburg, since its opening in 1912, has resigned on account of ill health.

Dr. Henry Albert, formerly professor of pathology and bacteriology in the University of Iowa, has resigned as director of the state hygienic laboratory in the University of Nevada to accept the position of state health commissioner in Iowa.

Dr. Edwin F. Hirsch, director of the Henry Baird Favill Laboratory in St. Luke's Hospital in Chicago, has been promoted to assistant professor of pathology in the University of Chicago (Rush Medical College).

At the Western Reserve University Medical School, Cleveland, Dr. Otto Saphir has been promoted to senior instructor in pathology for three years and Dr. Karl Krenz to instructor in pathology for two years.

Dr. James W. McElroy has been appointed instructor in pathology in the college of medicine of the University of Tennessee, Memphis.

First Award of Trudeau Medal.—The first award of the Trudeau Medal of the National Tuberculosis Association was made to Dr. Theobald Smith on Oct. 4, 1926, at the annual meeting of the association.

National Research Workers Accept Appointments.—Fellows in Medicine of the National Research Council have accepted appointments as follows to begin at the end of their fellowships:

Dr. William V. Cone, working with Dr. James W. Jobling in the department of pathology, College of Physicians and Surgeons, Columbia University, was appointed to a position in the department of surgery in the same institution.

Dr. Thomas P. Hughes, working with Dr. Hans Zinsser in the department of pathology, Harvard Medical School, was appointed assistant in bacteriology, the Rockefeller Institute for Medical Research.

Dr. Moses L. Isaacs, working with Dr. Frederick P. Gay in the department of bacteriology, College of Physicians and Surgeons, Columbia University, was appointed to a position in the Department of Public Health in the same institution.

James A. Kennedy, Ph.D., working with Dr. Hans Zinsser in the department of bacteriology, Harvard Medical School, was appointed instructor in bacteriology in the University of Rochester.

Dr. Beatrice Carrier Seegal, working with Dr. S. Burt Wolbach in the department of pathology of Harvard Medical School, was appointed pathologist to Long Island Hospital, Boston.

Dr. Fred W. Stewart, working with Dr. Frank B. Mallory, pathologic laboratory, Boston City Hospital, was appointed to a position in the Rockefeller Institute for Medical Research.

Meeting of Pathological Society of Great Britain and Ireland.—The next meeting of the Pathological Society of Great Britain and Ireland will take place on Jan. 7 and 8, 1927, at the School of Medicine for Women, Grays Inn Road, London, W. C. American pathologists will receive a hearty welcome.

Francis Harbitz of Oslo, Norway, Lectures.—Francis Harbitz, professor of pathology in the University of Oslo, Norway, gave the annual Gross Lecture of the Philadelphia Pathological Society, Oct. 11, 1926, on "Periarteritis nodosa."

Record of Blood Group Required.—It is reported that in Austrian hospitals the blood group to which the patient belongs must be recorded on the patient's history.

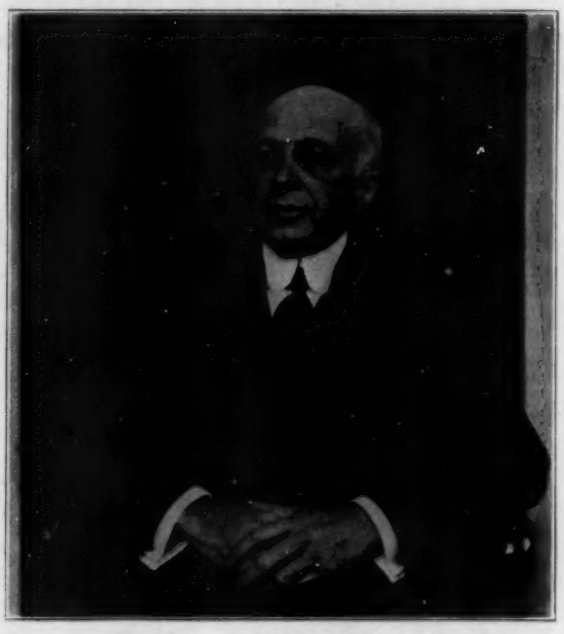
Massachusetts Medicolegal Society.—After a lapse of some years, the publication of the *Transactions of the Massachusetts Medico-Legal Society* has been resumed under the editorship of Dr. E. L. Hunt, Worcester, Mass. Number two of volume five has just appeared, and it contains several articles of medicolegal interest to pathologists.

Obituary

FREDERICK S. MANDLEBAUM, M.D.

1867-1926

Dr. Frederick S. Mandlebaum, aged 59, died on Aug. 7, 1926, as the result of an attack of subacute streptococcus endocarditis. He was born in Hartford, Conn. In 1889, he received his medical degree from the University and Bellevue Medical School. After serving as intern at Mount Sinai Hospital, New York, he spent two years in Berlin and Vienna, studying pathology under Virchow, Paltauf and Kolisko; hematology



FREDERICK S. MANDLEBAUM, M.D.
1867-1926

under Ehrlich; bacteriology in Koch's laboratory, and clinical medicine under Kraus and other masters. On his return in 1893, he became assistant pathologist at Mount Sinai Hospital in New York; in 1895, he was appointed pathologist and, later, director of laboratories. During this time the laboratory grew so rapidly that in 1904 a special building was devoted to it. Numerous physicians, both members of the hospital staff and others, received excellent training under him in the branches of pathology, bacteriology and chemistry.

The division of the routine work most interesting to him was surgical pathology, and in that line he was one of the great experts. He was a master of technical methods. His special studies were mainly on myasthenia gravis, tumors of the bladder, carcinoma of the appendix and splenomegaly.

Dr. Mandlebaum's place among pathologists is assured by his investigations on Gaucher's disease, which he pursued for more than twenty years, making fundamental contributions to the knowledge of this remarkable condition. He probably had more experience with this disease than any other pathologist, having made detailed studies of four cases of his own and of material from eight others. He was a pioneer in the chemical investigation of the specific Gaucher tissue. His results in this connection were of great importance in showing that if a cell stains with the usual iodized oil 40 per cent reagents it is not a Gaucher cell.

Dr. Mandlebaum was a charter member of the Association of American Pathologists and Bacteriologists, and a president of the New York Pathological Society. Because of his retiring disposition he responded to but few requests for presentations at meetings, but whenever he appeared, all were impressed by his dignified, courteous and kindly bearing.

E. LIBMAN.

Abstracts from Current Literature

Pathologic Physiology

NEW DATA ON DIFFERENTIAL FERTILITY IN THE UNITED STATES. RAYMOND PEARL, Am. J. Hyg. **6**:610, 1926.

On the basis of figures for 1923, it appears that in our population the professional, clerical, trade, domestic and personal service, public service and transportation-occupational classes are reproducing themselves in such a manner as to maintain about their present status, their relative representation in the population. But the heavy laboring classes, manufacturing, agriculture and mining classes are reproducing themselves greatly in excess of their representation in the population. (Full discussion of racial, social and economic importance in the complete paper.)

ETHEL B. PERRY.

BLOOD SUGAR IN STATUS THYMICOLYMPHATICUS: A NEW THEORY AS TO THE CAUSE OF SUDDEN DEATH. A. B. MACLEAN and R. C. SULLIVAN, Am. J. M. Sc. **171**:659, 1926.

Acute suprarenal insufficiency may be the immediate cause of death in status thymicolymphaticus.

ARTHUR LOCKE.

THE PATHOGENESIS OF DEATH FROM BURNS. H. M. GREENWALD and H. ELIASBERG, Am. J. M. Sc. **171**:682, 1926.

The cause of death from superficial burns in rabbits is shock followed by degenerative changes, particularly in the suprarenals.

ARTHUR LOCKE.

RESPIRATORY QUOTIENT CURVES IN DIAGNOSIS OF DIABETES. O. H. PETTY and W. H. STONER, Am. J. M. Sc. **171**:842, 1926.

"Respiratory quotient studies, before and every half hour for three hours after the administration by mouth of 1.75 Gm. of dextrose per kilogram of body weight, are a direct index of the normality or abnormality of the sugar-burning mechanism. By such respiratory quotient curves absolute differentiation may be made between diabetes mellitus and renal glycosuria, and diabetes mellitus may be diagnosed earlier than by the usual glucose tolerance test. A number of cases, whose blood sugar rose above 180 mg. per 100 cc. blood and returned to normal in less than three hours, were shown by respiratory quotient curves, to be definitely diabetic."

AUTHORS' SUMMARY.

EXPERIMENTAL STUDIES ON THE REACTING POWER OF ASTHENIC PERSONS, WITH SPECIAL REFERENCE TO THEIR ANTIBODY PRODUCTION. E. BARÁTH, Am. J. M. Sc. **171**:855, 1926.

Asthenic persons have a diminished reacting power toward irritants. The eosinophilia following injections of typhoid vaccine is absent or slight. The agglutinin production also is less than the normal, which may explain the old observation that asthenic persons are especially susceptible to infection.

ARTHUR LOCKE.

ARTERIOSCLEROSIS AND INCREASED BLOOD PRESSURE. F. R. NUZUM, B. SEEGAL, R. GARLAND and M. OSBORNE, Arch. Int. Med. **37**:733, 1926.

The authors mention five theories regarding the etiology of arteriosclerosis: (1) mechanical-physical theory, (2) chemical or infectious poisons theory, (3) metabolic theory, (4) theory of the predisposition of certain groups of poisons to degeneration of blood vessels, (5) theory of the disturbance of the acid-base balance resulting in the excretion of excessively acid amins and produced by high protein diet in both man and experimental animals. Feeding various excessive protein diets to experimental animals for periods as long as two years, the authors obtained increased blood pressures, and these animals presented extensive arteriosclerosis of the aorta and in many instances of the coronary arteries. The authors mention that increased blood pressure and arteriosclerosis can be produced without an increase of cholesterol in the diet.

S. A. LEVINSON.

RENAL COUNTERBALANCE. F. HINMAN, Arch. Surg. **12**:1105, 1926.

The article, which is virtually a monograph on the subject, deals with the question of anatomic and functional reserve power of the kidney. The keynote of the article is that there can be no permanent functional repair without a corresponding anatomic one. Part I deals with experimental work, and Hinman reviews at length the work of others as well as his own work. He deals successively with renal reserve, renal reparatory power, renal atrophy and renal counterbalance. Renal reserve is both anatomic and functional, and these go hand in hand, and are of two types, native and acquired. In the young, reparation is by hyperplasia and an actual increase in the number of secreting radicles occurs; but in the adult repair takes place by hypertrophy, the change affecting chiefly the glomeruli and convoluted tubules. Three main types are recognized, unilateral mass hypertrophy, such as follows nephrectomy; bilateral mass hypertrophy, brought about experimentally by ureteroduodenostomy; and a circumscribed or group repair, such as occurs in most renal diseases, the less injured areas compensating for the more severely attacked. True atrophy of disuse probably never occurs, renal atrophy being secondary to some prime factor. In two kidneys of unequal strength, the healthier will overcompensate and so counterbalance the inequality as to render the weaker kidney unnecessary, leading to a disuse atrophy. Part II is concerned with a clinical study of renal counterbalance, and the author points out that tests of renal function are empiric and give very poor indication of the actual anatomic conditions behind renal adjustments; at the present time there is no procedure to test renal reserve. Clinically there are four types of renal counterbalance: (*a*) unilateral, in which the power of one kidney replaces the loss of the other; (*b*) cooperative, in which both kidneys react to an increased demand; (*c*) competitive, in which there is an increased accumulation of work to one and gradual loss to the other, one grows while the other atrophies; (*d*) decompensation, in which there has been a maximum hypertrophy which is still unequal to the demand or in which the damage is so extensive as to prevent response to additional stimulus.

N. ENZER.

GASTRIC MOTILITY: THE MECHANISM OF THE PYLORUS. E. KLEIN, Arch. Surg. **12**:1224, 1926.

Klein passes in critical review the various theories of and experimental work on the mechanism of closure and opening of the pylorus beginning with Cannon's theory of "acid control." From the work of others he concludes that

this theory is inadequate, and from his own observations as well as those of many other workers, favors the mechanical theory as being most adequate and that fluidity of the stomach contents is a prime factor. His own experiments were those of direct observation on the stomach of dogs after food and after instillation of acid. These have been described previously. The pyloric ring is always in a state of tone, which is overcome by each peristaltic wave, with which the stomach contents are constantly being forced through to the duodenum regardless of whether the reaction is acid or alkaline. The pylorus contracts firmly only when the wave reaches it, when it is effectively closed. He observed that solid bodies are forced back into the body of the stomach until reduced to a fluid state. Solid particles may be carried over at the end of digestion when the pyloric tone is lowest.

N. Enzer.

The Effect of Sympathectomy on Spastic Paralysis of the Extremities. Loyal Davis and Allen B. Kanavel, J. A. M. A. **86**:1690, 1926.

Histologic evidence points to the dual innervation of skeletal muscle from the cerebrospinal sympathetic nervous systems. Experimental removal of the sympathetic trunks in cats produces no effect on normal tone that can be observed or recorded. The onset and maintenance of decerebrate rigidity in cats is unchanged after the removal of the sympathetic innervation to an extremity. With the exception of Royle's work on goats, the evidence in the literature is in agreement on this point. The problem of muscle tone is extremely complicated, and one or all of several mechanisms may be responsible for changes in muscle tone. At present there is no accurate clinical method for measuring changes in muscle tone. Lengthening and shortening reactions and "hung-up" reflexes alone are insufficient indications for operation. Kymographic tracings of tendon reflexes, faradic stimulation, active and passive motions and tremors before and after removal of the sympathetic nerve supply have shown no change in cases of paralysis agitans; postencephalitic Parkinson's disease; system degenerations of the spinal cord, such as lateral sclerosis, traumatic lesions of the spinal cord; cerebral hemiplegia, and Little's disease. The sympathetic nervous system may have some function dealing with the metabolism of muscle, so that under certain conditions the contractility of a muscle may be changed by the removal of sympathetic impulses. Such a function would probably be chemical in nature.

Authors' Summary.

Absorption from the Lower Respiratory Tract Under Normal and Pathologic Conditions. H. J. Corper, J. A. M. A. **86**:1739, 1926.

Dyes proved unsuitable for determining the comparative rate of absorption from various parts of the body because they cannot be subjected to accurate quantitative analysis and the appearance of the dye color in the skin or the blood stream of the experimental animal is subject to misinterpretation and error. For this reason sodium sulphocyanate was used as a test reagent in a concentration incapable of producing local injury, and absorption studied at different intervals by determining the quantity remaining at the site of introduction after different periods thus obtaining a curve depicting the rate of absorption under definite conditions and at different intervals. The rapidity of absorption of 2 cc. of 2 per cent sodium sulphocyanate from the lungs and pleura of guinea-pigs exceeds that from the peritoneum and subcutaneous tissues. Absorption is more rapid from the lungs than from the pleura, and

it is possible that absorption from the lungs in part accounts for the rapidity of absorption from the pleura. The rapidity of absorption of liquids from the lungs is probably to a great extent accounted for by the vascularity and large total surface of the terminal respiratory divisions. The absorption of sodium sulphocyanate by the pleura is not influenced by the presence of an artificial pneumothorax instituted shortly before and resulting in collapse of the lungs. Acute inflammatory conditions affecting the pleura, produced by chemical means (2 cc. of a 0.2 per cent solution of hydrochloric acid or 2 cc. of a 0.2 per cent solution of mercurochrome-220 soluble) retards the absorption of sodium sulphocyanate from the pleura. Acute inflammatory conditions of the pulmonary parenchyma, produced by gassing the animals with bromide one and three days prior to testing, retards the absorption of sodium sulphocyanate after intratracheal injection. The retardation of absorption from the pleura and the lungs is influenced by the grade of inflammatory changes present at the time of testing.

Absorption and resorption of liquids from the lower respiratory tract, the lungs and the pleura, follow the main principles of absorption in other parts of the body, but the anatomic structure and physiologic function lend to these tissues differences which exert an effect on the rate of absorption under normal and pathologic conditions.

H. J. Corper.

The Relative Reaction Within Living Mammalian Tissues: V. (a) Influence of Lymph Soluble Tissue Materials on the Significance of the Coloration with Some Phthalein Indicators. Douglas R. Drury and Peyton Rous, J. Exper. Med. **43**: 669, 1926.

The present paper is the first of two dealing with experiments which were planned to disclose the meaning of the colors assumed by mammalian tissues when vitally stained with some phthalein indicators. Derivatives of the tissues themselves were employed after tests had shown, in agreement with certain facts in the literature, that inferences from model experiments, so called, would be misleading.

Organs were perfused with water, or salt, or lymph of the same creature and extracted with small quantities of the fluid. The turbid extracts were colored with phthalein, the reaction determined colorimetrically with the aid of an arc light, and the findings were compared with potentiometer readings on the material. The results of the two methods were in close agreement.

The significance of the data will be discussed in the second paper.

Authors' Summary.

Studies of Hyperthyroidism: III. Bile Pigment Production and Erythrocyte Destruction in Thyroid-Treated Amphibian Larvae. C. C. Speidel, J. Exper. Med. **43**: 703, 1926.

Experimental hyperthyroidism in urodele larvae (*Amblystoma*) and anuran larvae (*Rana, Bufo,* and *Hyla*) is accompanied by definite changes in bile color. The normal pale green, or pale yellow-green, color of the full gallbladder changes progressively after thyroid administration to a brighter green, then to emerald-green, and finally to a very dark green. In several hundred observations no exceptions were noted.

The bile pigment, biliverdin (and its derivatives), is elaborated from the hemoglobin of worn out erythrocytes. Thyroid administration induces an

increased rate of erythrocyte destruction, and this is followed by an increased output of bile pigment. Other minor factors are mentioned which may modify the color of the bile to a limited extent.

Erythrocyte destruction occurs largely by enucleation, cytoplasmic segmentation, and fragmentation, and is probably widespread in the body. Many fragments and senile red cells collect in the liver. During the later stages of thyroid treatment, the macrophages becoming conspicuously active. They are especially abundant in the liver, in the intestine, and in the gills. In addition to the hemoglobin eliminated after transformation into bile pigment, some is transported by macrophages through the intestine lining, and to a less extent through the involuting gill epithelium, and thus eliminated from the body.

AUTHOR'S SUMMARY.

STUDIES ON UROBILIN PHYSIOLOGY AND PATHOLOGY: VI. THE RELATION OF BILIARY INFECTIONS TO THE GENESIS AND EXCRETION OF UROBILIN. PHILIP D. MCMASTER and ROBERT ELMAN, J. Exper. Med. **43**:753, 1926.

Experimental infection of the intubated and previously sterile biliary tract of the dog with particles of the stools leads to a formation of urobilin from the bilirubin of the bile as it flows through the ducts. No urobilinuria occurs, however, unless temporary biliary obstruction is produced, or the liver parenchyma is injured. Then urobilinuria develops, despite the fact that no bile is reaching the intestine and, by corollary, no urobilin is being formed there.

Cholangitic urobilinuria, as one may term the phenomenon just described, to distinguish it from the urobilinuria having origin in pigment absorbed from within the intestine, is far more pronounced in animals possessing a healthy gallbladder than in those with a pathologic gallbladder or with one prevented from functioning by severance of the cystic duct. These facts suggest that there may be an active absorption of urobilin from the normal gallbladder. There can be no doubt that the pigment is absorbed from within the bile ducts.

There is no evidence to justify the belief that urobilin is ever formed through the action of liver parenchyma. Conceivably, there may be an intralobular formation of the pigment consequent on the activity of bacteria within the liver tissue, although such a happening has yet to be demonstrated.

AUTHORS' SUMMARY.

THE INFLUENCE OF ASPHYXIATION ON THE BLOOD CONSTITUENTS OF MARINE FISHES. F. G. HALL, I. E. GRAY and S. LEPKOVSKY, J. Biol. Chem. **67**:549, 1926.

The blood volume becomes diminished and the concentration of the various blood constituents increased during asphyxiation. The implied transfer of water from the blood to the tissues may be due to the increased tissue acidity which accompanies asphyxiation.

ARTHUR LOCKE.

THE MINIMUM ENDOGENOUS NITROGEN METABOLISM. M. SMITH, J. Biol. Chem. **68**: 15, 1926.

A normal adult was placed in negative nitrogen balance. Only enough protein was given to prevent the diet of carbohydrate and fat from becoming intolerable. The restricted diet was maintained for twenty-four days without any apparent harmful effect to the subject. The average daily nitrogen excretion in the urine during this period was 3.34 Gm.

ARTHUR LOCKE.

EXPERIMENTAL PELLAGRA-LIKE CONDITION IN THE ALBINO RAT. JOSEPH GOLDBERGER and R. D. LILLIE, Pub. Health Rep. **41**:1025, 1926.

Rats with polyneuritic symptoms not too advanced can be cured by feedings of cornmeal extract (85 per cent alcohol extract dried on cornstarch), and with it as the only source of water-soluble B, peliagra-like, but no polyneuritic symptoms arise and growth is arrested. Both the symptoms and the arrest of growth can be remedied by supplementing the diet with as little as 6 per cent of the "P-P solid" from yeast (water extract of yeast heated two and one-half hours in the autoclave at 15 pounds' pressure, and adsorbed with fuller's earth), which is known to contain a preventive factor for the analogous conditions, pellagra in man and black tongue in dogs, but does not prevent polyneuritis. Like the cornmeal extract it does not, however, promote growth when used as the only source of water-soluble B in the diet. Seemingly then growth in rats depends on both the thermolabile antineuritic factor and a thermostable factor that is, possibly identical with the "P-P solid" preventive of black tongue and pellagra; and the so-called water-soluble B may include both factors, or even others. Realization of inadequate understanding of nutritional relationship impels reserved conclusions.

ETHEL B. PERRY.

THE FUNCTIONAL PATHOLOGY OF NEPHRITIS. E. B. MAYAS, Quart. J. Med. **75**:273, 1926.

On the basis that the kidney exercises two functions, filtration and concentration, Mayas accepts MacLean's classification of nephritis into hydremic and azotemic types. The former, primarily a disturbance of filtration, may develop hyposthenuria. In support of the theory that the chief cause of nephritic edema is failure of the plasma proteins to retain water in the circulation, Mayas devised a method of measuring the colloid osmotic pressure of the plasma proteins, which is exerted chiefly by serum albumin. He found that considerable changes in the salt content of the plasma had practically no effect on the colloid osmotic pressure, which, of course, does not support the view that chloride retention is of importance in the causation of edema. In hydremic nephritis the colloid osmotic pressure is reduced to a quarter of the normal value. The plasma in these cases contains less protein than normal serum, but the osmotic pressure is even lower than normal serum diluted to an equal protein content. In cardiac failure the edema occurs at a higher level of colloid osmotic pressure and appears to be due to an increase in capillary blood pressure from venous stasis and possibly from disturbance in nutrition of capillary endothelium as well. The depression of the freezing point and the concentrations of urea and chloride were determined in the plasma and urine of a number of patients with azotemic (chronic interstitial) nephritis. From his observations he concludes that there is no evidence of lessened permeability of the glomerular membrane to dissolved substances, but it is impossible to determine whether a sufficient number remain active to produce a normal amount of filtrate. The tubules are unable to concentrate the filtrate, although they are able in most cases to reabsorb the chlorides. The failure to concentrate the glomerular filtrate is due to a lowered osmotic resistance of the tubule cells to urea, allowing it to diffuse passively through them.

N. ENZER.

THE INHERITANCE OF EPILEPSY. W. BRAIN, Quart. J. Med. **75**:299, 1926.

In a series of 200 epileptic patients, 28 per cent gave a family history of the disease as compared with less than 10 per cent in a control series from a hospital population. In those with a family history the onset was earlier, and the family history was present more frequently in females. The author considers that this indicates that there is an inherited predisposition to the disease.

N. ENZER.

THE SPASM OF TETANY CONSIDERED AS A DISTURBANCE OF THE PHYSIOLOGY OF MUSCLE. J. P. MARTIN, Quart. J. Med. **75**:311, 1926.

The spasm of tetany is similar to that of myotonia. In tetany there is a reduction in blood calcium, and in many cases an alkalosis is present. Lactic acid and phosphoric acid are the immediate activators of muscle contraction, and these are derived from a precurser, lactacidogen. Calcium and reduced hydrogen ion concentration inhibit the production of these acids and they, therefore, will more readily be produced when the blood calcium is lowered and in the presence of alkalosis. He, therefore, considers that the spasm of tetany is due to a disturbance in the muscle metabolism and is not neurogenous.

N. ENZER.

HEREDITY OF DUPUYTREN'S CONTRACTION. G. SPROGES, Compt. rend. Soc. de biol. **94**:631, 1926.

Dupuytren's contraction was observed in seventeen of fifty-three persons, representing three generations of one family. Only two of the seventeen were women. Besides the palmar fascia, the sclerosis involved also the digital nerves, connective tissue and skin.

THE ROENTGEN-RAY IRRADIATION OF THE EGG AND EMBRYO. CULTURES IN VITRO. ANGEL H. ROFFO, Bol. Inst. med. Exper. **3**:143, 1926.

Cultures prepared from embryonic chick tissues soon after irradiation within the egg, even with large doses, developed as normal tissues; but if forty-eight hours intervened between irradiation and culturing, or even twenty-four hours if the embryo had been separated from the egg, the tissue was already in a state of disintegration, and development either failed or was weak. This behavior suggests that physicochemical and hormonic changes of the medium may result from the roentgen-ray treatment.

THE RELATION BETWEEN HYDROGEN ION CONCENTRATION AND SENSITIVITY TO IRRITATION. W. V. GAZA and BRANDI, Klin. Wchnschr. **5**:1123, 1926.

Intracutaneous injection of 0.2 cc. of isotonic phosphate buffer solution of p_H 7.2 causes no subjective annoyance except a slight feeling of pressure. Injections of similar solutions of p_H 7.4-8 are likewise painless. Solutions of a p_H less than 7.2 cause an active injection irritation which becomes almost unbearable at p_H 5.9. Irritation follows rapid injections only and disappears after a few seconds due to the buffer effect of the tissues. Intramuscular injection of the neutral and alkaline solutions is, similarly, not painful, while the acid solutions give rise to unpleasant sensations comparable to muscular fatigue.

ARTHUR LOCKE.

NITRATE DIURESIS. E. BECHER and G. MAY, Klin. Wchnschr. **5**:1229, 1926.

Nitrate diuresis is the result of an effect of sodium nitrate on the functioning of the kidneys.

ARTHUR LOCKE.

EXPERIMENTAL RESEARCHES INTO THE EXCRETION OF VARIOUS DISINFECTING AGENTS THROUGH THE BILE AND THEIR INFLUENCE ON BACTERIAL GROWTH IN THE BILE, BLADDER WALL AND LIVER. O. SPECHT, München. med. Wchnschr. **73**:809, 1926.

Methenamine, iodine, methylene blue and acriflavine are almost always, salicylic acid never, excreted into the bile. The presence of these disinfectants seems to have no influence on bacterial growth in the bile, liver or bladder wall.

ARTHUR LOCKE.

THE TESTING OF LIVER FUNCTION WITH AZORUBIN S. R. FENSTERMANN, München. med. Wchnschr. **73**:859, 1926.

Four cubic centimeters of 1 per cent azorubin S is injected intravenously. The quantity excreted with the urine is determined colorimetrically and parallels the degree of liver injury.

ARTHUR LOCKE.

FATAL AIR EMBOLISM AT THE BEGINNING OF AN EFFORT TO ESTABLISH AN ARTIFICIAL PNEUMOTHORAX. A. F. LINDBLOM, Acta med. Scandinav. **63**:301, 1926.

Fatal air embolism resulted from the needle entering a vein in the lung tissue in such a way that the air in the alveoli passed directly into the vein. The lung tissue about the track of the needle did not show any changes. There were general pleural adhesions.

Pathologic Anatomy

ETIOLOGY AND HEALING PROCESS OF DUODENAL ULCER IN MELENA NEONATORUM. R. L. J. KENNEDY, Am. J. Dis. Child. **31**:631, 1926.

Kennedy states that careful search will reveal peptic ulcer in a larger number of cases of melena neonatorum. In three cases, streptococci or diplococci were demonstrated in the tissues of the ulcers. It is believed that these must be the chief etiologic agents. Healing of duodenal ulcers begins early and proceeds rapidly, so that, under proper conditions, the injury may be repaired in a few days, an additional reason why they are difficult to find.

TORSION OF THE NORMAL FALLOPIAN TUBE. H. DARNER, Am. J. Obst. & Gynec. **11**:368, 1926.

Darner's case of torsion of the normal fallopian tube is the seventh on record occurring in nullipara. The patient, aged 13, had a sudden onset of pain in the right lower quadrant. The temperature was 100.6 F., and there was tenderness throughout the right lower quadrant, but no muscle spasm. Rectal examination under anesthesia revealed a sausage shaped mass in the right fornix. At laparotomy the distal third of the right tube was distended and bluish black. The middle and proximal thirds were twisted clockwise

three and one-half times. Microscopic studies of numerous sections showed no evidence of recent or old inflammatory lesions, no ectopic pregnancy or tumor. The appendix was normal.

A. J. KOBAK.

ENDOMETRIAL ADENOMA (IMPLANTATION) IN THE VERMIFORM APPENDIX. M. G. SEELIG, Am. J. Obst. & Gynec. **11**:461, 1926.

Seelig reports an endometrial implantation in the wall of the appendix removed from a nullipara, aged 27. The patient complained of severe cramps and moderate vomiting and diarrhea. A mass was felt in the right vaginal fornix, which at laparotomy was found to be the size of a hen's egg, located at the ileocecal junction and fused with the fimbriated end of the right tube. The appendix was coiled up on itself on the posterior wall of the cecum. Endometrial tissue was seen in its wall.

A. J. KOBAK.

VALVULAR DISEASES OF THE HEART WITH SPECIAL REFERENCE TO THE PATHOGENESIS OF OLD VALVULAR DEFECTS. B. J. CLAWSON, E. T. BELL and T. B. HARTZELL, Am. J. Path. **2**:193, 1926.

In addition to the vegetations in acute endocarditis there is a diffuse inflammation always in the free edge and often involving the greater part of the leaflet. This circumstance explains the uniform thickening so commonly seen in old defective valves.

Rheumatic vegetations are composed chiefly of fibroblasts, and in the process of healing they readily become converted into fibrous tissue. There is no ulceration and no organization. Fifty-five of seventy-three old defective valves are considered the result of rheumatic endocarditis, and in twenty-seven of these, incompletely healed rheumatic lesions were recognizable.

Bacterial endocarditis is a more intense inflammation than the rheumatic. Proliferation predominates, but exudation is often prominent. Large thrombi are formed on the raw surfaces, and there is often ulceration. Healing consists in the conversion of the leaflet into scar tissue. Such portions of the thrombi as do not become detached persist indefinitely without becoming organized, although they may become calcified. Complete healing rarely occurs. Three of seventy-three old defective valves were interpreted as the result of bacterial endocarditis.

Transitions between rheumatic and bacterial vegetations are frequently seen. Rheumatic vegetations were found in association with bacterial in three-fourths of the cases of subacute bacterial endocarditis.

Fifteen of seventy-three old defective valves belong to the aortic calcified nodular group. The etiology of this type is unknown. There is no satisfactory evidence that it is of inflammatory origin, and it seems unrelated to atheroma. Aortic stenosis, in the absence of disease of any other valve, is usually of this form.

Stenosis is more frequent than insufficiency in old defective valves. The only pulmonary valve defects seen were of the congenital type (three cases of pulmonary stenosis).

An acute rheumatic endocarditis may terminate in several different ways: (*a*) death during the acute stage from toxemia; (*b*) partial or complete healing followed after a variable interval by the reappearance of fresh rheumatic vegetations (recurrent rheumatic endocarditis); (*c*) partial or complete healing

followed by the formation of bacterial vegetations on the valves—a more active inflammation (subacute bacterial endocarditis); (*d*) slow incomplete healing giving rise to deformed leaflets on which rheumatic inflammation is still recognizable; (*e*) complete healing resulting in thickened, stiffened valves with smooth surfaces.

As to pathogenesis, old valvular defects in seventy-six hearts are interpreted as follows: fifty-five were caused by rheumatic endocarditis, three by bacterial endocarditis, fifteen (all aortic stenosis of the calcified nodular type) of undetermined origin and three (pulmonary stenosis) congenital.

AUTHORS' SUMMARY.

A STUDY OF THE ACCESSORY PANCREAS WITH REPORT OF ONE CAUSING CONGENITAL PYLORIC STENOSIS. K. HALE, Ann. Surg. **83**:774, 1926.

Microscopic sections through the pylorus in a case of congenital pyloric stenosis revealed the presence of aberrant pancreatic tissue in the hypertrophic muscle coat. The author believes that the presence of this pancreatic tissue was the direct cause of the stenosis.

N. ENZER.

RETICULATED RED CELLS. W. DAMESHEK, Boston M. & S. J. **194**:759, 1926.

An analysis of the red blood cells in forty-nine cases of pernicious anemia is presented. The reticulate count of the red cells is regarded as a true index of bone marrow activity. Before and at the beginning of any remission or permanent rise in red count, the reticulate count surpasses 6 per cent; as the culmination of the rise is reached, it gradually falls to normal (from 0.5 to 1 per cent). With bone marrow aplasia, the reticulate count is extremely low. There is no better index to prognosis in pernicious anemia than the count of the reticulated cells. Although these are frequently increased, and 5 per cent probably represents regeneration going on in the face of greater destruction, a sudden rise in count to more than 6 per cent presages a coming remission, overbalancing destructive forces. Grave are the continued low counts that bespeak forthcoming death. The relapse in pernicious anemia is closely related or, at least, extremely similar to aplastic anemia, which with its evident bone marrow failure, has almost no reticulate cells. Platelet regeneration and aplasia are apparently closely related to red cell growth, for in purpura hemorrhagica the reticulate count goes up before recovery and remains low with impending death from hemorrhages. In diagnosis, the marked reticulosis in congenital hemolytic anemia is a pathognomonic point differentiating that disease from all other anemias accompanied by a large spleen.

THE RELATION OF THE RETICULO-ENDOTHELIAL SYSTEM TO THE BLOOD PLATELET COUNT. HARRY KOSTER, J. Exper. Med. **44**:75, 1926.

So-called blockade of the reticulo-endothelial system results in a marked increase in the platelet count. The count rapidly becomes high and shows a sharp partial recoil and then a gradual diminution, even though the blockade is continued. The mechanism regulating the number of platelets is complicated. Apparently phagocytosis by cells of the reticulo-endothelial system is not the only means by which blood platelets are destroyed.

AUTHOR'S SUMMARY.

RELATION BETWEEN ORGAN WEIGHTS AND OBSCURE LESIONS IN APPARENTLY NORMAL RABBITS. WADE H. BROWN, LOUISE PEARCE and CHESTER M. VAN ALLEN, J. Exper. Med. **44**:85, 1926.

A study of organ weights was made on a group of 295 normal rabbits for the purpose of determining whether any relation could be detected between the weights of organs and the extent and activity of the lesions found post mortem.

The results obtained seemed to indicate that disease, even in its mildest form, is capable of affecting the weights of organs that are not directly involved by the disease process, and that the effect produced bears a relation to both the extent and the activity of the lesions present. There was also some evidence that the converse might be true; namely, that the occurrence and subsequent course of disease may be influenced in some measure by the state of organ balance and the ability of the animal organism to adjust itself to meet the demands of disease producing agencies.

AUTHORS' SUMMARY.

MICROSCOPIC STUDIES ON CAPILLARY INNERVATION AND STAINING OF THE ENDOTHELIAL CELLS. I. S. BARKSDALE, J. Lab. & Clin. Med. **11**:1053, 1926.

The blood capillaries in the frog's tongue are innervated by contiguity with the nerve fibrils rather than by continuity with them. The arterioles, on the other hand, are innervated not by contiguity, but by continuity with the nerve fibrils. Five-tenths cubic centimeter of a 1 per cent solution of indigo-carmine, injected subcutaneously, stains the capillary endothelium a bluish gray. The same effect may be obtained with an intracardial injection of 0.3 cc. of the same solution. Examination of the stained capillary endothelium with the oil immersion lens reveals neither a thickening of the cells during capillary constriction nor a thinning out during dilatation.

S. A. LEVINSON.

A RETICLE OF ENDOTHELIAL CELLS IN THE THYROID AND PARATHYROID. G. SCOTT WILLIAMSON and INNES H. PEARSE, J. Path. & Bact. **29**:167, 1926.

A reticle of endothelial cells in the thyroid and parathyroid bodies is described. The cells of this net are coarsely granular and basophilic, and under certain conditions appear as large stellate granular cells. They are believed to function in much the same way as the Kupffer cells of the liver. It is found that the cytoplasmic contents of the reticulo-endothelial cells vary with changes in the functional activity of the thyroid and parathyroid glands.

E. M. HALL.

"CALCIFICATION" IN THE RABBIT'S BRAIN. C. DA FANO and J. R. PERDRAU, J. Path. & Bact. **29**:195, 1926.

In the brains of two rabbits which had clinically recovered from herpetic encephalitis, an incrustation of nerve cells and deposition of granular or globular material had taken place. Both processes occurred in areas showing severe destructive and infiltrative changes. The histologic picture was suggestive of calcareous degeneration, but microchemical tests showed that the deposits were due to the precipitation of iron salts on necrotic nerve cells.

E. M. HALL.

RUPTURE OF THE UTERUS DURING PREGNANCY. J. RIDDEL, J. Obst. & Gynec. Brit. Emp. **33**:1, 1926.

Riddel reviewed twenty cases of rupture of the uterus and added one of his own. He found that rupture of the uterus occurs more frequently in multipara, and that previous injury, infection, chronic inflammation and operative scars are predisposing factors. Slight forms of violence may start the rupture. Rupture occurs frequently in the fifth month and in the upper portion of the fundus, often at the site of placental implantation, so that invasion by the chorionic villi may be another factor in weakening the uterine wall. The diagnosis is based on a symptomatology of acute abdominal involvement with signs of internal hemorrhage.

A. J. KOBAK.

BRONCHOPULMONARY SYPHILIS (EXACT STATE OF OUR ANATOMICROPATHOLOGIC KNOWLEDGE). S. I. DE JONG, Ann. d'anat. path. et d'anat. norm. méd.-chir. **3**:193, 1926.

In this rather important memoire de Jong brings up to date the accumulated material concerning the pathologic condition of pulmonary syphilis.

Lesions in the lungs found at necropsies and believed to be of syphilitic origin are characterized by him as follows: (1) isolated pulmonary gummas of various sizes—small, as observed by himself, and agglomerated caseated masses described by Professor Letulle; (2) white pneumonia of the new-born which in a large number of cases is due to a grave congenital syphilis, but which may also be of tuberculous origin; (3) the most important lesion is that of an extensive pulmonary sclerosis with marked bronchiectasis, and the presence of gummas visible either with the naked eye or on microscopic examination. The latter group is also characterized by lesions in which macroscopic or microscopic gummas are accompanied by sclerotic changes around the anterior bronchi and pulmonary alveoli; (4) the outstanding lesion is a dilatation of the bronchi. This affects at least one lobe which is transformed into a fibrosed and indurated block having a honeycombed appearance, as a result of bronchiectasis.

According to Professor Letulle, pulmonary syphilis is noticeable by its focal character, by its property to attack the bronchi rather than the blood vessels and by its tendency to affect invariably the lymphatics. The lesion produced by the *Spirochaeta pallida* is either follicular interstitial or bronchopneumonic in type. Both lesions are frequently associated and progress either toward organization with an abundance of avascular connective tissue or toward the formation of fibrosis without traces of anthracosis.

De Jong is of the opinion that bronchopulmonary syphilis undoubtedly exists. In the present state of our knowledge it is, however, of a rather limited importance from a broad clinical point of view, as well as from the standpoint of the pathologic condition of the lungs.

B. M. FRIED.

ON TISSUE CULTURES OF THE LUNG. F. J. LANG, Arch. f. exper. Zellforsch. bes. Gewebezücht. **2**:93, 1925.

From the study of tissue cultures of rabbit's lung, the following conclusions are reached:

1. The alveolar phagocytes are to be regarded as ameboid, phagocytic histiocytes of connective tissue origin, identical with the macrophages of Metchnikoff and the polyblasts of Maximow. This is in opposition to the currently accepted view that these cells represent freed nucleated epithelial cells.

2. To the extent that cells of this kind form part of the alveolar wall, they do so as connective tissue cells of marked developmental potentiality. Their surface relationships may be those of epithelial cells, but their original location is in the interstices of the reticulo-endothelial system.

3. In accordance with the views of Maximow and of Aschoff and Kiyono, there is distributed over the entire adult vertebrate body a peculiar cell strain, which takes no part in the development of specific structures, but which retains unrestrictedly all of the potentialities of embryonic mesenchyme. While this may show different structural characteristics in different portions of the body, it has everywhere the power to develop into histiocytic elements. The interstitial tissue of the alveolar wall forms part of this system.

4. Part of these septum cells lie at the edge of the septum as the so-called "nucleated epithelium"; others, the proportion depending on circumstances, are mobilized as actively ameboid phagocytes. With sufficient proper irritation, all of the septal mesenchyme may be mobilized in this way.

5. No evidence was found of a true alveolar epithelium, aside from the nonnucleated platelets. These, the writer conjectures, may be renewed by shifting of the bronchial epithelium.

H. E. Eggers.

Embolic Papillary Nephritis. C. Artusi, Beitr. z. path. Anat. u. z. allg. Pathol. **75**:1, 1926.

Artusi reports a case of acute necrotizing papillary nephritis following pharyngeal angina and pyemia in a child, aged 3½ years. The lesion was characterized by necrosis and purulent infiltration of the papillae of the renal medulla. Bacterial emboli were present in the vessels of the involved tissue. The author believes it is necessary to recognize two types of papillary nephritis, an excretory form first described by Orth, due to the localization in the papillae of bacteria which have been excreted into the tubules, and a rarer embolic form in which the bacterial localization is within the blood vessels.

O. T. Schultz.

The Reticulum of Lymph Nodes. F. Orsós, Beitr. z. path. Anat. u. z. allg. Pathol. **75**:15, 1926.

The author devotes 121 pages to a detailed description of the reticulum of normal lymphadenoid tissue and to the changes which occur in various disease processes. The normal reticulum is a cellular protoplasmic syncytium within which fibrils are formed. Some of the latter become transformed into collagenous others into elastic, fibrils. The course of the fibrils and the thickness of the fibril bundles is in part due to the functional activities of the tissue, and in part to mechanical factors brought about by the lymphoid and other cells and by the lymph and blood channels embedded in the reticular syncytium. The reticular system takes a part in pathologic changes which occur in lymphadenoid tissues; in some processes it plays the chief rôle. The reaction may be degenerative or proliferative, the former resulting in rupture and destruction of fibrils, the latter in an increase in the amount of fibrillar substance and in sclerosis of the tissue. In the formation of tubercles in lymphadenoid tissue, the reticulum cells take the most important part.

O. T. Schultz.

NEUROVASCULAR ORIGIN OF APPENDICITIS. S. RUF, Beitr. z. path. Anat. u. z. allg. Pathol. **75**:135, 1926.

On the basis of personal examination of normal and early acutely inflamed appendixes, Ruf refutes the theory of Ricker that the primary factor in acute appendicitis is stimulation of the nerves of the blood vessels, which leads to stasis and to vascular injury, following which the injured tissue becomes infected by bacteria from the lumen. Ricker had also claimed that the normal appendix exhibits active peristalsis. Ruf could see no peristaltic activity in appendixes examined in situ, in abdominal operations, nor could he find any evidence, by microscopic examination, of vascular changes which might be supposed to antedate the focal mucosal changes present.

O. T. SCHULTZ.

REGENERATION AND PIGMENT FORMATION IN LIVER TRANSPLANTS. G. HERXHEIMER and G. JORNS, Beitr. z. path. Anat. u. z. allg. Pathol. **75**:157, 1926

The central portions of small subcutaneous autotransplants of liver tissue in rabbits rapidly undergo necrosis. The bile capillaries, filled with bile, can still be recognized on the fourteenth day by means of the Eppinger stain. At the periphery of the transplants some regeneration of liver cells occurs, sometimes with the formation of syncytial masses. Bile canaliculi are not formed by the regenerated cells, and the latter do not regain the power of forming or excreting bile. They are able, however, to store glycogen. The interlobular bile duct epithelium proliferates and forms new ducts, but the latter never give rise to liver cells, a fact which leads the authors to assume that the bile ducts can take no part in regeneration of the liver. The regenerated liver cells contain large amounts of pigment, believed to be formed within the cells. This material is not bile pigment. It stains with sudan III, gives the other reactions of the lipochrome-like metabolic pigments, and belongs to the group of "wear and tear" (Abnutz) pigments.

O. T. SCHULTZ.

PSEUDOLEUKEMIA, LYMPHOSARCOMA, LYMPHOGRANULOMA AND THEIR VARIOUS RELATIONSHIPS. S. M. ZYPKIN, Folia Haemat. **32**:33, 1925.

The author believes that the majority of diseases of the blood-forming organs are fundamentally related. These organs react to irritants in three stages, if the irritation is continued and sufficiently severe. These three stages are called the pathologic triad. In the order of their occurrence they are: (1) degeneration of parenchyma, (2) proliferation of parenchyma, (3) proliferation of stroma. Thus, the aleukemias (pseudoleukemias) with their leukemic phases, together with the lymphosarcomas, represent the second stage. Hodgkin's disease, in its early or cellular form, also belongs in this stage, while its late or scirrhous form typifies the third stage. Embryonalization of both stroma and parenchyma in these conditions is considered one of the chief reasons for their relative malignancy. In the more benign diseases of the lymphatic and hematopoietic organs the irritation is more transitory, and this embryonalization does not occur. The term "pseudoleukemia" should apply only to the aleukemias. Banti's disease is a pseudoleukemia in which the splenic fibrosis represents a third stage change, while the cellular marrow belongs to the second stage. Previously reported and new cases, many of which are transitional in type, are cited in support of these interpretations.

C. J. WATSON.

HISTOLOGIC STUDY OF A CASE OF MYELOID LEUKEMIA, WITH MEASUREMENT OF THE MITOTIC ANGLES. SVEND PETRI, Folia Haemat. **32**:103, 1926.

The author reports a case of chronic myelogenous leukemia in a man, aged 61. At necropsy, the bone marrow was similar to that of pernicious anemia, in that there was marked erythropoietic activity. Using Ellermann's technic, he was able to substantiate the latter's method of differentiating between early, nongranular forms, some of which were pregranulocytic myeloblasts, while others were spoken of as erythrogonia.

Measurement of the angles of mitotic figures in fifty neutrophile myelocytes and forty myeloblasts gave an average reading of 68 degrees, while with the so-called erythrogonia (forty measurements) the average reading was only 22 degrees. A special instrument called the goniometerocular was used in measuring these angles.

C. J. WATSON.

CHANGES IN THE VEGETATIVE NERVOUS SYSTEM IN SYPHILIS. B. MOGILNITZKY, Virchows Arch. f. path. Anat. **259**:489, 1926.

Mogilnitzky examined the peripheral and central vegetative nervous system in fifteen cases of syphilis with the aim of detecting changes which he thought may explain certain of the manifestations of syphilis, such as focal canities, the Argyll-Robertson pupil, tabetic crises, etc. In the sympathetic ganglions he describes proliferation of the interstitial stroma, perivascular lymphocytic infiltration, and degeneration of the ganglion cells, and in the vegetative portion of the central nervous system necrobiosis of individual ganglion cells and focal demyelinization. The changes described were much the same in both early congenital and late acquired syphilis, although the symptomatology of the two groups was not identical.

O. T. SCHULTZ.

AN ORGANIC LESION OF THE CENTRAL NERVOUS SYSTEM FOLLOWING PARATYPHOID B INFECTION. A. JAKOB, Virchows Arch. f. path Anat. **254**:450, 1925.

Jakob reports a case of severe intestinal infection in which paratyphoid B was cultured from the blood. Neurologic symptoms of generalized hypertonicity and choreiform movements were observed with dysarthria and complete disorientation. Pathologically, a severe subacute parenchymatous degeneration was found. The anterior central gyrus, the prefrontal area, striatum, dentate nucleus and olives suffered greatest, although changes were found in the entire brain. In the cortex, layers III and V and the Betz cells were severely degenerated, and of the basal ganglions the large striatal cells were mostly degenerated. The ganglion cells were swollen and revealed marked fatty degeneration. The protoplasmic glia cells were proliferated, and glia roset formations were present. The glia and endothelial lining of the vessels contained an excess of lipoid material. There was a partial secondary degeneration of the pyramidal tract. There was a marked resemblance in the clinical picture and in the pathologic observations to spastic pseudosclerosis. Jakob believes that pseudosclerosis may be a group of various toxic infectious conditions giving the same clinical syndrome.

ROY GRINKER.

ACUTE ANTERIOR POLIOMYELITIS. W. WÖHRMANN, Virchows Arch. f. path. Anat. **259**:466, 1926.

Wöhrmann describes the cord changes in a case of poliomyelitis in a girl aged 19 years. Death occurred within twenty-four hours of the earliest paralytic manifestations, and the case is considered important because the

alterations noted are believed to be the earliest recorded. The changes were limited to the gray matter of the cord and especially to that of the anterior horn. Ganglion cells were degenerated, but there was no neuronophagy at this early stage. There was marked cellular infiltration, with a predominence of polymorphonuclear leukocytes which gave the oxidase reaction. Lymphocytes and large mononuclear cells were also present. The author concludes that poliomyelitis is a true inflammatory process, not primarily a degenerative one, and that in the inflammatory reaction leukocytes are more numerous than has previously been held to be the case.

O. T. Schultz.

Arterial Changes in Gangrene of the Extremities. H. Borchardt, Virchows Arch. f. path. Anat. **259**:521, 1926.

Borchardt made a microscopic study of the arteries in spontaneous gangrene of the lower extremities, using the material from seventeen cases in which gangrene was a complication of diabetes and seven cases without diabetes. He also studied the same vessels in five cases of diabetes not complicated by gangrene. He concludes that spontaneous gangrene is the result of obliterating intimal proliferation, which is associated with medial degeneration and calcification. Gangrene is much more frequent in diabetic than in nondiabetic patients, and in the former occurs at an average earlier age than in the latter. In the diabetic patients without gangrene, arterial changes are also marked and diabetes is looked on as an important etiologic factor in medial degeneration of the peripheral arteries.

O. T. Schultz.

Pseudocystic Degeneration of Thymus. K. Löwenthal, Virchows Arch. f. path. Anat. **259**:531, 1926.

In a poorly nourished woman, aged 32, who had suffered for fourteen years with articular rheumatism, the thymus was hypertrophied. It contained numerous small cystlike spaces which were not true cysts but areas of hydropic degeneration. The condition is looked on as an abnormal form of involution of the thymus.

O. T. Schultz.

Pathologic Anatomy of Arterial Hypertension. H. Borchardt, Virchows Arch. f. path. Anat. **259**:549, 1926.

In ten cases of clinical hypertension Borchardt found widespread arteriocapillary fibrosis and arteriosclerosis, but his investigation did not permit him to say whether the hypertension or the vascular change was primary. He concludes that the pathologic anatomist is as yet not in a position to affirm or deny the contention of clinicians that there occurs a condition of essential hypertension without vascular change or one in which the vascular changes are secondary to increased pressure.

O. T. Schultz.

Pseudohermaphroditism and Suprarenal Hyperplasia. E. Feldmann, Virchows Arch. f. path. Anat. **259**:608, 1926.

To the considerable number of reported cases of pseudohermaphroditism, usually of the external feminine type, associated with suprarenal cortical hyperplasia, Feldmann adds a case in a child, aged 7 years, who died of bronchopneumonia. In his case also the cortex of each suprarenal was hyperplastic.

Feldmann believes that in the female the internal genitalia, derived from the müllerian and wolffian duct systems, and the external genitalia, derived from the urogenital sinus, may differentiate in opposite directions, the internal genitalia developing normally, the external abnormally, under the influence of increased suprarenal cortical function.

O. T. SCHULTZ.

GIANT CELLS IN MYELOID LEUKEMIA. K. KÖRNER, Virchows Arch. f. path. Anat. **259**:617, 1926.

Körner describes a case of acute myeloid leukemia in a man, aged 68, the striking feature of which was the presence of large numbers of giant cells in the liver, spleen and lymph nodes and of smaller numbers of similar cells in other organs. The giant cells were of the megakaryocyte type. The author believes that they arose locally in areas of myeloid metaplasia.

O. T. SCHULTZ.

HITHERTO UNDESCRIBED BODIES IN BONE MARROW. A. PLEHN, Virchows Arch. f. path. Anat. **259**:628, 1926.

In the fresh bone marrow of general paralytic patients who had been inoculated with malaria, and later in that of persons who had never had malaria or syphilis, Plehn found round and ovoid bodies whose diameter varied from one-third to one-half that of a red blood corpuscle. They were finely granular, the granules taking a grayish blue with the Giemsa stain. Their origin and relation to the cells of the marrow could not be determined. The author claims that these bodies have never before been described; he names them P-bodies, using the initial of his surname.

O. T. SCHULTZ.

RARE LESIONS OF THE SPLEEN. W. ROTTER, Virchows Arch. f. path. Anat. **259**:631, 1926.

This is a casuistic report of a case of periarterial iron and calcium incrustation of the spleen and one of circumscribed nodular splenitis. The author believes that the first condition is the result of hemorrhage from damaged trabecular arteries. The process which led to the formation of a single large fibrous nodule within the spleen in the second case could not be determined. The tissue was believed to be inflammatory in origin.

O. T. SCHULTZ.

ANOMALY OF POSITION OF APPENDIX. H. KÖHLER, Zentralbl. f. Chir. **53**:1115, 1926.

The appendix arose from the ileum 2 cm. from the ileocecal valve.

NECROSIS IN TH. HYPOPHYSIS. E. J. KRAUS, Ztschr. f. Hals-, Nasen- u. Ohrenh. **14**:14.,

Necrosis in the hypophysis has been discovered to be a not uncommon lesion as a result of the systematic examination of large series of hypophyses. In spite of its rich blood supply, the anterior lobe is the site of infarcts. These are usually located in the lateral portions of the lobe and are frequently bilaterally symmetrical. The middle and posterior lobes appear to be immune to infarction. The importance of infarction of the hypophysis is due to the

frequency with which hypophysial cachexia follows extensive destruction of the anterior lobe. The most frequent cause of necrosis in this organ is embolism associated with puerperal sepsis and ulcerative endocarditis. Kraus reports ten cases, illustrating less common causes, as follows: perihypophysial infiltration with metastatic sarcoma involving the cavernous sinus; interstitial hypophysitis in a congenitally syphilitic infant; endartertis associated with diabetes mellitus; and seven cases in which thrombophlebitis of the veins of the hypophysis accompanied an acute suppurative or gangrenous perihypophysitis.

J. P. Simonds.

On the Share of the Heart and Vessels in Human Trichinosis. Georg B. Gruber, Zentralbl. f. Herz u. Gefässkrankh. **17**:1, 1925.

Basing his conclusions on a local epidemic of four cases, the writer interprets the marked circulatory disorders observed in the light of the investigations of trichinosis by Flury and Groll. Accordingly he views most of the phenomena as the result of intoxication from the liberation of toxic cleavage products from the attacked muscle. The edema of trichinosis he regards as of dual origin —early, from injury to the vessel walls by the intoxication, late, following cardiac intoxication. Lowering of blood pressure he conjectures may likewise result in part from direct intoxication, or from this plus central intoxication, with cardiac atony playing a part in the later stages. As regards the cardiac lesions themselves, they do not appear to be connected with the presence of the parasites. While it is probable that they invade the heart early in the disease, the parasites seldom settle here, and practically invariably have left the heart long before the onset of the maximum myocardial reaction, which occurs in the fifth and sixth weeks of the disease. The character of the tissue reaction is that of an early focal infiltration with lymphocytes, plasma cells and eosinophils. Later lymphocytes alone dominate the picture. Healing takes place without scarring, the cellular exudate disappearing apparently by absorption.

H. E. Eggers.

Ova of Paragonimus Westermanii Encysted in Abdominal Wall. P. D. Choy and A. I. Ludlow, China M. J. **40**:326, 1926.

Paragonimus ova were present in the sputum and feces. Following an attack of fever marked by loss of appetite and constipation the patient suffered severe pain in the epigastrium, accompanied by a swelling in the same region which persisted and increased in size slowly until it was 6 cm. in diameter. The growth was slightly bluish and fairly soft. It was vascular and adherent to both skin and the muscle fascia. In the vascular connective tissue stroma were found the ova of *Paragonimus westermanii.*

Pathologic Chemistry

The Significance of Cholesterol in Tropical Hydrocele. H. M. Stenhouse, Am. J. Trop. Med. **6**:143, 1926.

The author notes the high incidence of hydrocele in the hospitals of St. Croix, one of the Virgin Islands. There it is from thirty to forty times more common than in the United States. Arteriosclerosis, cataract and elephantiasis appear frequently and at an early age. *Filaria bancrofti* infects practically the entire population.

Filarial embryos are not present in the majority of hydrocele fluids while cholesterol crystals are found frequently. The author believes that the filarial parasites alter cholesterol metabolism to a greater extent than any other infectious agent. The mechanism of hydrocele formation, he conceives to be due to plugging of outlet stomas in the endothelial lining of the tunica vaginalis by cholesterol crystals.

Cholesterol in weak aqueous solution was injected into the tissues of a rabbit's leg. Swelling, fibrosis and lymphatic obstruction resulted. In a similar manner, elephantoid tissue in man may result from lymphatic obstruction due to cholesterol. The author discusses the significance of high cholesterol content of body tissues in relation to arteriosclerosis.

E. M. Hall.

The Adsorption of Nitrogen by Hemoglobin. J. B. Conant and N. D. Scott, J. Biol. Chem. **68**:107, 1926.

A part of the nitrogen dissolved in hemoglobin solution is "physically dissolved" or adsorbed. Experimental investigations of the oxygen-hemoglobin system should consider the possibility that a part of the dissolved oxygen may be similarly adsorbed.

Arthur Locke.

The Electrodialysis of Human Blood Serum. A. Bernhard and J. J. Beaver, J. Biol. Chem. **69**:113, 1926.

Human blood serum was placed in the central compartment of an electro-osmotic cell containing fixed, noncirculating quantities of distlled water in the electrode compartments. The sodium and potassium were found to be completely removed from the serum into the cathode chamber, but calcium, magnesium, and phosphorus were found to be only partly removed and to appear in both cathode and anode chambers, at the time of examination.

Arthur Locke.

Ketosis in Pregnancy. V. J. Harding and K. D. Allin, J. Biol. Chem. **69**:133, 1926.

The threshold of ketonuria in pregnancy is the same as in the nonpregnant condition. Diets which theoretically should produce a large excretion of acetone may produce only a ketonuria slightly above the threshold value. In calculating the ketogenic-antiketogenic balance in pregnancy attention should be paid to the raised metabolism occurring in the latter half of gestation. The urinary nitrogen may be unexpectedly low, thus reducing the antiketogenic factor.

Authors' Summary.

Epinephrin Shown Chemically in the Blood. Determination Differentiating Epinephrin from Glucose in the Blood. H. Friend, J. Lab. & Clin. Med. **11**:950, 1926.

Epinephrine is shown to be a normal constituent of the blood stream. A determination is offered to differentiate between the epinephrine and the actual glucose content of the blood. An attempt is made to demonstrate the difference between true hyperglycemia and hyperepinephrinemia; for example, epinephrine added to human blood is shown to increase the color intensity of the blood-sugar reagent, which color is diminished almost to the color of the original

sugar content after treatment with ferric chloride. (Pure glucose is shown to be unaffected by ferric chloride.) This is further shown by injections of epinephrine hydrochloride into human subjects. The blood pressure is shown to rise. There is an increase in the color density of the blood sugar and then on addition of the ferric chloride to the same filtrate the color density diminishes. Glucose does not react in this manner. A new normal blood sugar figure is suggested. Such substances as uric acid, creatinine, creatine, glucuronic acid, lactose and purines, which might interfere (add to) with the blood sugar determination were found to be unaffected after treatment with ferric chloride.

S. A. Levinson.

Some Thoughts and Experiments in Relation to the Hormones: The Crystallization of Insulin. John J. Abel, Proc. Inst. Med., Chicago **6**:108, 1926. Crystalline Insulin. John J. Abel, Proc. Nat. Acad. Sc. **12**: 132, 1926.

Commercial insulin contains 80 per cent or more noninsulin substance. According to a previous report (Researches in Insulin: I. Is Insulin an Unstable Sulphur Compound? J. J. Abel and E. M. K. Geiling, *J. Pharmacol. & Exper. Therap.* **25**:423, 1925), repeated precipitation with sixth normal pyridine and redissolving with sixth normal acetic acid; grinding of the precipitate with phenol (about 90 per cent); recovering the active part from the phenolic supernatant with ether, alcohol or water, precipitating and finally separating the insoluble portion, leaves the acetic-acid-soluble, comparatively pure insulin "fraction 4." From a solution of acetic acid of this fraction the contaminating substance was precipitated with brucine (6 Gm. in 95 cc. sixth normal acetic acid) and the insulin precipitated by sixth normal pyridine. The crystals thus formed may be washed with distilled water, redissolved in acetic acid and reprecipitated as before; or they may be dissolved in fifteenth molar disodium hydrogen phosphate and then acidulated drop by drop with sixth normal acetic acid and left standing for slower precipitation which yields larger crystals. Insulin crystals are doubly refractive, of the rhombohedral division of the hexagonal system, melt sharply at 233 C., give a biuret reaction and positive Millon's, Pauly and ninhydrin tests, are soluble in dilute alkalis and acids but not in distilled water, and are easily rendered inert by boiling in tenth normal sodium carbonate (or sulphuric acid) which liberates the labile sulphur which seems to parallel quantitatively the hypoglycemic potency of the extract. As little as 0.01 mg. per kilogram of this purified insulin lowers the blood sugar of a rabbit to approximately the convulsive level of 0.045 per cent.

E. B. Perry.

On the Macro-Chemistry of the Endodermis. J. H. Priestley and E. Rhodes, Proc. Roy. Soc., Series B, **100**:119, 1926.

As the result of macrochemical methods of investigation the following statements may be made about the endodermis: The primary endodermis contains free fat and other fatty derivatives, in some form of combination, yielding on saponification normal and oxidized fatty acids. In its secondary and tertiary stages the endodermis contains suberin-like materials similar to those found in potato cork. As in potato cork, the suberin lamella arises from fatty substances as the result of oxidation and drying processes. The relative increase

in the combined insoluble fatty anhydrides as in the case of regenerated potato cork, appears to take place at the expense of free fat or fatty acid. The basal substance of the Casparian strip contains no nitrogen, but some substance containing nitrogen and sulphur is closely knit into the fabric of the strip.

AUTHORS' SUMMARY.

THE REGULATION OF THE ACID-BASE EQUILIBRIUM. K. GOLLWITZER-MEIER, Klin. Wchnschr. **5**:737, 1926.

This article is a review of the subject.

ARTHUR LOCKE.

THE HISTOCHEMICAL DETECTION OF PHOSPHATE AND OTHER IONS IN GROWING BONES. W. STOYE, Klin. Wchnschr. **5**:791, 1926.

The bone fragment is secured soon after death, cut at least twice along the long axis, and soaked in a solution of 3 to 4 per cent ferric chloride or, preferably, 0.2 to 0.3 per cent uranium acetate in 5 per cent, well-neutralized formalin for from twenty-four to forty-eight hours, with several changes of the solution and occasional agitation. It is then thoroughly washed in running water, decalcified with a 5 per cent solution of acetic acid containing some formalin, and embedded in celloidin or paraffin. The visibility of the precipitated ferric or uranyl phosphates may be increased by immersion of the section in freshly-prepared, weakly acid (1 to 2 per cent acetic) 2 per cent ferrocyanide solution, when the pale yellow, crystalline precipitates become an intense blue and red-brown, respectively. The dissolved phosphate concentration is greatest in the outer part of the cartilage proliferation layer and in the outer part of the periosteal cambium layer, while the maximum dissolved calcium concentration (method of Rabl) is in the inner part of these two layers. Calcification is probably, in its first phase, a binding of phosphate ion to protein derivatives, and in its second phase, a formation of calcium protein phosphate; the bone growth commencing with a phosphate accumulation in the osteogenic issues followed by calcium accumulation. In growing bones, the bony diaphysis is covered with a layer of available calcium which is in turn overlaid with a source of available phosphorus. The "dissolved" phosphate ions are probably derived from the available organic combinations by an enzyme-splitting action. The enzyme or its activator may be identical with the antirachitic principle.

ARTHUR LOCKE.

THE DIAGNOSIS OF PREGNANCY AND THE DETERMINATION OF SEX WITH THE AID OF INTERFEREOMETRY. H. KLEESATTEL, Klin. Wchnschr. **5**:796, 1926.

The results are entirely negative.

ARTHUR LOCKE.

THE QUANTITATIVE DETERMINATION OF PROTEIN WITH TANNIN AND ITS USE FOR THE DIAGNOSIS OF CANCER. R. WIGAND, München. med. Wchnschr. **73**:521, 1926.

The concentration of protein and protein-like substances in a solution may be estimated indirectly by precipitation with tannic acid. A series of dilutions is examined for the production of a turbidity with the tannic acid reagent. That dilution in which turbidity is just manifest corresponds approximately to a protein dilution of 1:1,000,000.

ARTHUR LOCKE.

THE PHOSPHORUS FRACTIONS OF THE BLOOD. H. HEINELT, München. med. Wchnschr. **73**:729, 1926.

The tissues have a capacity for storing phosphorus in the form of an acid-soluble complex.

ARTHUR LOCKE.

STUDIES ON UREA NITROGEN CONCENTRATION OF THE BLOOD: PART III. THE EFFECT OF THE VEGETATIVE SYSTEM ON THE BLOOD UREA NITROGEN CONCENTRATION. KASANU TASHIRO, Tohoku J. Exper. Med. **7**:221, 1926.

When the peripheral stump of the vagus is stimulated or the parasympathetic stimulants, such as pilocarpine and choline, are administered, the blood urea nitrogen and residual nitrogen contents are increased. On the contrary, if atropine is given, these nitrogen substances decrease more or less. If atropine is used together with pilocarpine, the augmentative action of the latter is arrested. The stimulation of the central stump of the vagus lessens the blood urea nitrogen and residual nitrogen contents, in opposition to the stimulation of the peripheral stump of the nerve.

After the injection of epinephrine hydrochloride, the stimulation of the splanchnics, or piqûre, the blood urea nitrogen and the residual nitrogen contents rather show a tendency to decrease.

When the vagus is stimulated in a rabbit with extirpated spleen, the blood urea nitrogen increases while the blood residual nitrogen content does not increase, but rather decreases.

When the vagus of nephrectomized animals is stimulated, the residual nitrogen content of the blood increases, but the urea nitrogen content does not and the amino acids fraction increases.

The blood of the liver vein contains apparently more urea nitrogen than that of the portal vein or artery. In opposition to this, the blood of the portal vein contains a much greater quantity of amino acids fraction than that of the liver vein or artery.

AUTHOR'S SUMMARY.

Microbiology and Parasitology

EXPERIMENTAL RAT-BITE FEVER. M. THEILER, Am. J. Trop. Med. **6**:131, 1926.

A spirochete closely resembling *Spirochaeta morsus-muris* was demonstrated by Theiler in the blood of guinea-pigs and white mice injected with the blood from a typical human case of rat-bite fever. White mice and rats are readily infected with the spirochete. These animals show no symptoms but harbor the organism in the blood for a long time. Guinea-pigs inoculated with the spirochete, after an incubation period of from six to fifteen days, develop fever, enlargement of the lymph glands, inflammation and later induration of the external genitals, and loss of hair. Rabbits were infected by subcutaneous, intradermal and intratesticular injection of blood containing the spirochetes. About half of the animals used developed no symptoms but their blood was infective for guinea-pigs for three weeks after inoculation. In the serum of infected rabbits, strong spirocheticidal properties are developed. It is noteworthy that spirochetes have been found in only a small number of cases of rat-bite fever. The intestinal tract of guinea-pigs normally contains large numbers of spirochetes and it is possible that they may enter the circulation

from time to time. The fever in guinea-pigs injected with blood from patients with rat-bite fever is not paroxysmal and the injected guinea-pigs do not appear to develop any eruption as is the case in the human disease.

A Case of Influenza Bacillus Endocarditis. Ella Hutzler Oppenheimer, Bull. Johns Hopkins Hosp. **38**:372, 1926.

The case, while caused by the Pfeiffer bacillus, clinically shows the protracted course, cardiac disease, splenomegaly, hemorrhagic nephritis, eruption, fever and clubbing of the digits, with an onset suggestive of a cerebral accident, so characteristic of *Streptococcus viridans* disease. Anatomically, the type of the vegetations on the chronically diseased and thickened valves, the widespread petechiae, the infarcts and the embolic nephritis fit in detail into the same picture.

Author's Summary.

Prophylaxis and Treatment of Wound Infections by Modern Methods. K. F. Meyer, California & West. Med. **24**:145, 1926.

The prophylaxis of tetanus and gas gangrene is discussed by Meyer on the basis of 148 cases in California between June, 1922, and March, 1925. Nineteen were cases of tetanus neonatorum, suggesting that a primitive type of delivery is still practiced in certain strata of the population; vaccination was followed by tetanus in two instances; there were eight cases of postoperative tetanus. As few instances of catgut infection have been proved, Meyer says it is more reasonable to suspect the intestinal canal of the patient himself as the source of postoperative tetanus. Since it is established that tetanus spores or any gas gangrene producing anaerobe ingested on raw vegetables may multiply in the intestinal tract and remain there in large numbers, the surgeon should fully appreciate this insidious source of wound infection before he suspects his surgical instruments, sutures and dressings. The data emphasize anew the well known fact that relatively trivial injuries may lead to tetanus. Only three, possibly four, persons who received puncture wounds, lacerations, contusions or compound fractures of the type considered most liable to tetanus infection had the benefit of a prophylactic injection of antitoxin. The majority of the patients involved never consulted a physician, and either ignored the injuries or treated them by unknown remedies. On the other hand, at least five physicians failed to give antitoxin, although the character of the injury (compound fracture, deep nail puncture) should have aroused suspicion of the possible consequences. Furthermore, the prophylactic treatment was not conducted in accordance with established practice, and, Meyer says, one is forced to conclude that those responsible were not familiar with the basic principles of the prevention of tetanus.

Abnormal Bacterial Flagella in Cultures: Their Resemblance to Spirochetes. Hideyo Noguchi, J. A. M. A. **86**:1327, 1926.

Besides the leptospira-like filaments, probably originating from red blood corpuscles under certain conditions in vitro, other spiral elements exist which may be erroneously interpreted as spirochetes. These are the exaggerated detached flagella of certain bacteria, produced under cultural conditions. In cultural studies of micro-organisms, the occurrence of these spiral elements must be borne in mind, particularly in connection with dark field illumination.

Spirochetes belonging to the *Spironema* and *Treponema* groups also produce, under certain cultural conditions, exaggerated flagellar appendages. These

terminal flagella are similar in appearance and structure to the axial spiral filaments of the same organisms, but are much finer. The axial filaments are covered with a layer of cytoplasm which can be removed by the action of bile. The motility of these organisms resides in the portion of the filament next the attachment of the flagellum at either end.

The great resemblance which exists between the flagella of motile bacteria and the flagellar and axial spiral apparatus of certain spirochetes seems to indicate that the axial filiaments are probably a modified apparatus of similar origin especially adapted to the locomotion of spirochetes and therefore supports the hypothesis of a close phylogenic relationship between bacteria and spirochetes.

AUTHOR'S SUMMARY.

STUDIES ON PNEUMOCOCCUS GROWTH INHIBITION. V. THE RELATION OF VIRULENCE TO THE PNEUMOCOCCIDAL ACTIVITY OF NORMAL RABBIT SERUM-LEUKOCYTE MIXTURES. SHUTAI T. WOO, J. Exper. Med. **43**:623, 1926. VI. THE SPECIFIC EFFECT OF PNEUMOCOCCUS, SOLUBLE SUBSTANCE ON THE GROWTH OF PNEUMOCOCCI IN NORMAL SERUM-LEUKOCYTE MIXTURES. RICHARD H. P. SIA, J. Exper. Med. **43**:633, 1926.

By testing the power of mixtures of serum and leukocytes to destroy pneumococci, it was found that the rabbit serum-leukocyte mixtures could kill nonvirulent pneumococci but had no effect on virulent pneumococci. In the young rabbit the blood was found to have no destructive effect on pneumococci.

A small amount of purified soluble substance of pneumococci reduced the pneumococcidal action of serum-leukocyte mixtures so that even a small number of a virulent pneumococci could grow freely. This action of the soluble substance was found to be specific for each pneumococcus type. In other words, the effect of the soluble specific substance of pneumococci in the serum-leukocyte mixture is to confer on virulent pneumococci of the corresponding type the capacity to growth of a virulent pneumococcus.

THE GEOGRAPHICAL DISTRIBUTION OF SPONTANEOUS ENCEPHALITIS IN RABBITS. E. V. COWDRY, J. Exper. Med. **43**:725, 1926.

The observations reported in this paper seem to justify the hope that the obstacle afforded to experimentation by the frequent presence of spontaneous encephalitis and nephritis in American and European rabbits does not exist to the same degree in rabbits from certain other localities. The observations are, furthermore, despite their obvious limitations, in conformity with the theory that the disease is not one common to domestic rabbits everywhere but rather that it occurs in special localities from which, given favorable conditions, it may spread. Thus far it has not been reported in tropical climates or south of the equator.

AUTHOR'S SUMMARY.

STUDIES ON REGENERATION OF BACTERIOPHAGE. II. THE INFLUENCE OF OXYGEN UPON THE BEHAVIOR OF BACILLUS COLI TOWARDS LYTIC PRINCIPLE. GREGORY SHWARTZMAN, J. Exper. Med. **43**:743, 1926.

The investigations of the influence of oxygen on the bacteriophage phenomenon recorded in this paper show that this factor plays an important rôle which is due exclusively to its ability to induce certain changes in the behavior of bacterial cells toward lytic principle. At certain hydrogen ion concentra-

tions both aerobic and anaerobic cultures can be made resistant in the absence of lytic principle. The resistance thus acquired is of a stable nature under suitable conditions. If the lytic principle is added to aerobic or anaerobic types of resistant strains the cultures are able to regenerate it to a certain extent. However, they do not undergo any visible lysis themselves even under the action of lytic principles which were passed through several generations of these types. The principles regenerated by both types of resistant cultures are identical in action with each other as well as with the stock lytic principle.

These experiments suggest a new method of investigation into the hitherto unexplained nature of resistance of bacteria toward bacteriophage.

AUTHOR'S SUMMARY.

INHALATION EXPERIMENTS ON MICE WITH PNEUMOCOCCI. F. GRIFFITH, J. Hyg. **25**:1, 1926.

Fatal general infection was readily produced in mice by spraying with pneumococcal culture in a closed chamber. No artificial means of lowering the animals' resistance was employed. Vaccination by subcutaneous and intraperitoneal inoculation with heated cultures gave protection against infection by inhalation to eleven of thirteen mice. Passive immunity, induced by an injection of homologous antipneumococcal serum immediately before spraying, gave complete protection. A large proportion of the mice which survived spraying were nasopharyngeal carriers a fortnight later and the condition persisted in one mouse for ninety-nine days. The development of an immunity in the carriers was not determined, but there was no indication that the state of immunity influenced the carrier condition.

ARTHUR LOCKE.

THE BACTERIAL FLORA OF MARKET OYSTERS. J. C. GEIGER, WINNEFRED E. WARD and M. A. JACOBSON, J. Infect. Dis. **38**:273, 1926.

No *B. typhosus* was found in 784 samples of shucked and 328 samples of shell oysters examined at the time of the recent epidemic in Chicago.

Several organisms were found which were closely related to the members of the paratyphoid-dysentery group. We are not able to classify these organisms definitely, however, in this group by all cultural or specific serologic reactions.

It is of interest to note that some of these organisms were agglutinated completely in a dilution of 1:400 by an antityphoid serum of high titer.

AUTHORS' SUMMARY.

EXPERIMENTS ON THE PURIFICATION OF CULTURES OF SPIROCHAETA PALLIDA BY CHEMICAL METHODS. DOROTHY WILKES-WEISS and CHARLES WEISS, J. Infect. Dis. **38**:281, 1926.

Experiments were undertaken to determine the selective inhibitory action of various germicidal substances on the growth of bacteria which may contaminate cultures of *Spirochaeta pallida*.

The following chemicals are satisfactory (in the dilution and time of exposure stated) for the purpose of destroying *B. coli* as well as *Staphylococcus aureus* without affecting the viability of the reproductive power of *Spirochaeta pallida:* selenium oxychloride or tricresol (in a 1:100 dilution, to be used for one minute); trichloracetic acid (1:100 for fifteen minutes), or formaldehyde (1:20 for five minutes).

When it is desired to destroy staphylococci alone, a larger variety of chemicals may be employed: gentian violet, acid fuchsin, mercurochrome, mercurophen, methylene blue, monarsone, neo-arsphenamine, atoxyl, acid arsphenamine, antiformin, Lugol's solution (iodine), ethylhydrocuprein hydrochloride or neosilvol.

AUTHORS' SUMMARY.

WASSERMANN REACTION IN SYPHILIS OF RABBITS. RUSSELL D. HERROLD, J. Infect. Dis. **38**:290, 1926.

Observations of the Wassermann reactions in experimental syphilis of rabbits indicate that the serologic response is not identical in every instance. There is also a vacillation in the reaction to some extent. The results in rabbits suggest that if repeated Wassermann tests were made in cases of suspected latent syphilis, many patients might be found to be syphilitic whose syphilis is now overlooked.

AUTHOR'S SUMMARY.

A STUDY OF DÖDERLEIN'S VAGINAL BACILLUS. ABRAHAM F. LASH and BERTHA KAPLAN, J. Infect. Dis. **38**:333, 1926.

The term "Döderlein's vaginal bacillus includes a large group of organisms which, though related, have some differentiating characteristics. This fact makes it difficult to classify them.

Among the mediums used the most favorable for cultivating these organisms was found to be 1 per cent lactose in neutral broth.

Lactobacillus vaginae, a provisional name for the Döderlein strain B studied has never previously been described.

The exacting cultural requirements and the incidence of the organisms in the normal vaginas of the new-born and adults are facts on which the hypothesis is based that Döderlein's vaginal bacillus has a function in inhibiting the growth of pathogenic organisms by direct action or by maintaining certain conditions in the vagina by its action on the vaginal mucous membrane.

AUTHORS' SUMMARY.

SOLUBLE TOXIC PRODUCTS OF THE ENTERITIDIS-PARATYPHOID B GROUP AND THEIR ACTION ESPECIALLY IN RELATION TO BLOOD SUGAR. MAUD L. MENTEN, J. Infect. Dis. **38**:354, 1926.

Soluble toxic substances derived from organisms of the enteritidis-paratyphoid B group produce alterations in the blood sugar and morphologic lesions which are identical with those produced by injection of the living or killed bacteria.

On intravenous injection of the toxic substances, a series of blood sugar curves are obtained which are proportional to the amount of the substance injected. The characteristics of these curves, which have been divided into three groups, are discussed.

A second injection after an interval of less than two weeks causes modifications of the hyperglycemic and hypoglycemic curves obtained with a single injection.

The toxic substance is thermostabile, soluble in water and can be precipitated by alcohol and concentrated acetic acid.

AUTHOR'S SUMMARY.

THE ORGANISM OF ACTINOMYCES-LIKE TONSILLAR GRANULES. RUTH TUNNICLIFF, J. Infect. Dis. **38**:366, 1926.

From an actinomyces-like tonsillar granule a weakly gram-positive, flexible, motile anaerobic organism has been isolated that produces in pure culture rosets and test-tube brushlike forms similar to those seen in the original material.

AUTHOR'S SUMMARY.

HEMOLYTIC STREPTOCOCCI OF THE BETA TYPE IN CERTIFIED MILK. HOWARD J. BROWN, W. D. FROST and MYRTLE SHAW, J. Infect. Dis. **38**:381, 1926.

Beta hemolytic streptococci in considerable numbers were found in the certified milk of five dairy herds. These streptococci belonged to several distinct cultural and serologic groups. There is no evidence that any of them, whether from cows with garget or from mixed milk, are pathogenic for human beings. The causative organism of milk-borne septic sore throat is *Streptococcus epidemicus*. This streptococcus is probably of human origin but occasionally may gain entrance to the udder of a cow and find its way into the milk supply. The hemolytic streptococci commonly found in milk show distinct cultural and biologic differences from *Streptococcus epidemicus*. No single test, however, can be relied on to differentiate them. All the tests are of value. A few bovine strains may possess capsules. Many produce rapid hemolysis of blood cells in fluid mediums. A considerable number are markedly pathogenic for mice. Many ferment the same sugars as the human strains. A few produce about the same final hydrogen ion concentration in glucose broth as do the human strains and a few resemble the latter in producing little or no hydrolysis of sodium hippurate. The latter two tests, however, are probably the most constant and reliable of those tried.

A routine procedure for the detection of *Streptococcus epidemicus* in milk may be outlined as follows:

Milk should be inoculated into poured blood-agar plates.

Capsules should be looked for in moist india ink preparations from young moist surface colonies.

Deep colonies with beta zones of hemolysis are to be fished into serum broth. To save time fishings from the same colonies may be made into glucose broth and into sodium hippurate broth.

Tests may be made with the broth culture as follows: (*a*) A hemolysin test is made by adding 0.5 cc. of a 5 per cent suspension of washed rabbit blood corpuscles to 0.5 cc. of broth culture, and taking care not to contaminate the broth culture so that it may be used for subsequent tests. Cultures producing little or no hemolysis in two hours at 37 C. may be discarded and subsequent tests omitted. (*b*) A stock culture is made on a blood-agar slant. Capsules should be looked for again after incubation over night. (*c*) Sodium hippurate broth is inoculated if it has not already been inoculated directly from the colony. By means of the ferric chloride test hydrolysis of sodium hippurate may be detected in from twenty-four to forty-eight hours. (*d*) Glucose broth is inoculated if it has not already been inoculated directly from the colony. The final hydrogen ion concentration should be determined in not less than forty-eight hours. (*e*) Salicin and mannite broths are inoculated. Saccharose, lactose and raffinose have seldom been found of value for this differentiation. (*f*) Mice are inoculated, although this test has been found less significant than the others.

To justify condemnation of the milk the streptococcus found should correspond in all respects with the characters of *Streptococcus epidemicus.*

AUTHORS' SUMMARY.

STUDIES ON SNUFFLES IN RABBITS. ASAZO TANAKA, J. Infect. Dis. **38**:389, 1926.

The nasal secretions, blood and lung exudates from rabbits with snuffles contain some organism pathogenic for mice and rabbits, but the filtrates from these materials are not pathogenic. *Bacterium lepisepticum* was isolated in pure culture in the majority of cases; *Bacillus bronchisepticus* was also isolated in pure culture, but in fewer cases.

Other bacteria were observed in less abundance in the blood or exudates of rabbits with snuffles. From the heart blood of animals dying after being injected with snuffles material, either *Bact. lepisepticum* or *B. bronchisepticus* was always isolated.

For mice and rabbits the virulence of *Bact. lepisepticum* and *B. bronchisepticus* is high, the latter, however, being less virulent than the former.

The strains of *Bact. lepisepticum* or *bronchisepticus* from rabbits with snuffles show a close relationship immunologically to the serum of those rabbits in which identical organisms were demonstrated in abundance, while other organisms less numerously present do not show such a relationship.

The isolated strains of *Bact. lepisepticum* and *B. bronchisepticus* are agglutinated by the respective antiserums, but do not show cross agglutination. The biologic characters of the isolated strains of *Bact. lepisepticum* or *B. bronchisepticus* are identical with those of the type strains received from other laboratories.

Snuffles identical with natural snuffles was produced in rabbits experimentally with strains of either *Bact. lepisepticum* or *B. bronchisepticus.*

The leukocyte count in the rabbit's blood was found to decrease immediately after injection with *Bact. lepisepticum, B. bronchisepticus* or *Bacillus influenzae,* remaining low for a few hours and then increasing so as to reach normal within forty-eight hours. This fluctuation was conspicuous in the pseudo-eosinophils.

In four spontaneous subcutaneous abscesses, *Bact. lepisepticum* was demonstrated in pure culture; the abscess strains were identical with *Bact. lepisepticum* strains from rabbits with snuffles. The serum of rabbits having abscesses possessed a certain amount of immune agglutinin for the autogenous strain and for stock strains of *Bact. lepisepticum.* Subcutaneous abscesses were produced experimentally by the injection of an abscess strain and of a lung strain of *Bact. lepisepticum. B. bronchisepticus* was not found in the abscesses in these cases.

Sinusitis accompanied most cases of snuffles in rabbits. *Bact. lepisepticum* and *B. bronchisepticus* were the predominant organisms in the sinusitis, the strains appearing to be identical with the snuffles strains of these organisms.

AUTHOR'S SUMMARY.

A COMPARATIVE STUDY OF PASTEURELLA CULTURES FROM DIFFERENT ANIMALS. ASAZO TANAKA, J. Infect. Dis. **38**:421, 1926.

Hemorrhagic septicemia bacteria isolated from various animals show a marked similarity in their biochemical, cultural and morphologic characteristics. This limited systematic classification which finds acceptance among workers in this country differs somewhat from that advanced in Europe.

No evidence was found, by means of the agglutination and complement fixation reactions, of indicated specific host differences among these organisms, although it is quite possible that group differences may occur.

The invasive power of these organisms is usually high, particularly when freshly isolated, and especially for certain animals, notably the rabbit. Their antigenic power is low as measured by the immunity stimulated in the animal and by immunologic reactions in vitro.

AUTHOR'S SUMMARY.

THE PRODUCTION OF EXPERIMENTAL ENDOCARDITIS WITH PNEUMOCOCCI AND STREPTOCOCCI IN IMMUNIZED ANIMALS. HEDLEY D. WRIGHT, J. Path. & Bact. **29**:5, 1926.

Mair (1923) found endocarditis in seven of ten rabbits which had received a series of injections of autolyzed pneumococci followed two months later by a series of gradually increasing doses of living pneumococci, some of which were highly virulent.

Wright immunized nineteen rabbits by intravenous injections of autolyzed broth cultures of pneumococci, each rabbit receiving twenty-eight injections over a three months period. Eleven animals survived this treatment. The antibody content of the serum was small. After a rest of three weeks seven animals were selected for treatment with living cultures of pneumococci. During five weeks the injections were gradually increased from 1 cc. to 5 cc. three times weekly. None of the rabbits developed endocarditis.

In another experiment five rabbits in various stages of immunization were given intravenously 5 cc. of a twenty-four hour broth culture of living pneumococci on each of three successive days. One rabbit not previously immunized died of septicemia; two which showed low antibody content developed endocarditis, one an aortic lesion, the other a mitral lesion; another developed arthritis; one animal remained well

Following this the author tried a similar experiment using eleven treated rabbits. None developed endocarditis.

In experiment 3 a more virulent strain of pneumococci was used—twelve animals were immunized over a period of three months, followed by a rest of eight weeks after which living cultures were injected as before. One rabbit developed endocarditis, two died of intercurrent infections the others showed no lesions. Later, nine rabbits were treated with gradually increasing doses of living pneumococci without preliminary immunization, from twenty to thirty doses being given over a period of four months. None of the rabbits developed endocarditis.

Wright next tried injections of nonhemolytic streptococci all the strains but one having been isolated from cases of subacute infective endocarditis. In all, twenty-two rabbits received each a single dose of 5 cc. intravenously of a twenty-four hour broth culture. One rabbit developed endocarditis of the mitral valve and died in seven days. Fifteen of the rabbits were then given repeated injections intravenously of 5 cc., some every second day, others weekly. Three animals developed endocarditis, in one case accompanied by arthritis. The author concludes that endocarditis may be produced by injections of pneumococci into immunized animals as shown by Mair and that it may also be produced by repetition of relatively innocuous doses of streptococci, but the occurrence seems to be fortuitous and unpredictable.

The lesions produced consisted of voluminous vegetations composed largely of thrombus with a cellular reaction of the acute type. No increase in fibrous tissue was noted.

There is evidence of marked antibody production by such animals which at the same time show a progressively increasing septicemia such as is found in subacute infective endocarditis in man.

E. M. Hall.

Investigations of the Etiology of Acute Polymorphous Erythema: Streptobacillus Moniliformis. C. Levaditi, S. Nicolau and P. Poincloux, Presse méd. **34**:340, 1926.

One of the authors developed an acute septicemia accompanied by erythema, sore throat and involvement of the joints. After a sudden onset, the disease developed in three attacks within twelve days. The defervescence in each attack was followed by a papulo-erythematous eruption, predominantly on the legs. The presence of two nodules on the forearm completed the picture of a combination of erythema nodosum and acute erythema multiforme. In blood cultures a new germ developed, which they call *Streptobacillus moniliformis*, and which was highly virulent for rabbits, guinea-pigs and other animals, localizing particularly in the skin and joints.

The Effects of a Solution of Pathologic Tissues and of Tubercle Bacilli in Salts of Cerium. A. Simonini, Boll. d. Ist. sieroterapico, Milan **5**:15, 1926.

Orange red cerium ammonium citrate [$Ce(NO_3)_4NH_4NO_3$] can, under certain conditions, dissolve organized cells (tubercle bacilli) and organized tissue (glands, etc.). The solutions of tubercle bacilli and pathologic tissues, rubbed into the normal skin on the flexor surface of the forearm of patients, produced severe general and local reactions, which disappeared soon, and often had a far-reaching effect on the illness. The effects were not strongly specific.

B. R. Lovett.

Local Immunity and Vaccination by the Enteric Route in Typhoid and Paratyphoid. M. Lusena and G. Rovida, Boll. d. Ist. sieroterapico, Milan **5**:19, 1926.

The authors wished to test the hypothesis that immunity in intestinal infections is local. They attempted immunization of rabbits by mouth, but the results were too irregular to admit of definite conclusions. Some of the animals became immune, and others hypersensitive. This hypersensitiveness, which may occur during immunization by the parenteral route also, is regarded as being a manifestation of an anaphylactic type. The authors conclude that the usual experimental animals are not suitable for this work, and that experiments in immunizing by this method would have to be carried out during an epidemic in order to confirm the hypothesis.

B. R. Lovett.

The Filtrability of Tuberculous Virus. G. Dessy, Boll. d. Ist. sieroterapico, Milan **5**:41, 1926.

The author could not confirm the filtrability of tuberculous virus. The attempt to pass tuberculous material through Berkefeld N filters failed. Eight guinea-pigs into which filtrates had been injected showed no sign of infection. The tuberculin test on these animals was negative. Cultures on Petroff's medium, glycerine bouillon and potato were sterile.

B. R. Lovett.

ACIDOPHILS. KARL SCHLIRF, Centralbl. f. Bakteriol. O., I **97**:104, 1926.

To call all the organisms isolated from the mouth, caries, vagina, milk, etc. "acidophils" is not correct. He terms them "acidotolerant." An acid medium is not necessary for their cultivation, and not always correct. He used a liver-liver-broth medium for isolation. He classified them as *Acidobacterium laetis, aerogenes, moroi, doederleinii* and *bulgaricum*. For their classification, the morphology, especially "width of the rods," is important; further, form on agar, gelatin, reaction of milk, gas or no gas production and degree of acidity in sugar medium.

E. E. ECKER.

PRODUCTION OF VITAMIN BY BACTERIA. W. KOLLATH and B. LEICHTENTRITT, Centralbl. f. Bakteriol. O., I **97**:119, 1926.

It was impossible to prevent scurvy in the guinea-pig by feeding the animals *B. coli*, mixture of bacilli from the intestines of the guinea-pig, or the Friedländer's bacillus (living or killed at 56 C.) or by the medium itself. Experiments therefore demonstrate that the growth stimulating factors for influenza bacilli are not the same as the real vitamins.

E. E. ECKER.

OPTIMUM HYDROGEN-ION CONCENTRATION (p_H) AS THE MOST IMPORTANT DISINFECTING FACTOR IN LOCAL AND GENERAL INFECTIONS AND ITS SIGNIFICANCE FOR THE TREATMENT OF PURULENT PERITONEAL INFLAMMATIONS. F. KEYSSER and O. ORNSTEIN, Klin. Wchnschr. **5**:404, 1926.

The maximum bactericidal action of disinfecting solutions is exerted within a limited p_H range determined by the character of the organism and of the disinfecting agent. Substances which are highly bactericidal in vitro may be but little active in vivo because buffering effects prevent the maintenance of optimum p_H.

ARTHUR LOCKE.

PATHOLOGIC BACTERIAL COLONIZATION IN THE DUODENUM AND ITS CAUSAL FACTORS. W. LÖWENBERG, Klin. Wchnschr. **5**:548, 1926.

A lack of hydrochloric acid is a favoring but not essential factor for the colonization of pathogenic organisms in the duodenum. The normally present bactericidal action of the duodenal fluid is essential for the protection of this part of the intestine against bacteria. Inflammatory diseases of the bile passages may be associated with a diminution of this bactericidal function.

ARTHUR LOCKE.

ON XYLOSE-FERMENTING AND XYLOSE-NONFERMENTING STRAINS OF TYPHOID BACILLI. O. HARTOCH, H. SCHLOSSBERGER and W. JOFFE, Ztschr. f. Hyg. Infektionskrankh. **105**:564, 1926.

Of sixty-six freshly isolated strains of typhoid bacilli and eleven old cultures, fifty-five fermented xylose; twenty-two cultures did not attack xylose. No serologic differences could be detected between the strains that fermented xylose and those that did not, and there were no differences in the clinical course of the disease caused by the two groups. Repeated pure cultures of typhoid bacilli from the same patient all reacted in the same way with respect to xylose.

MULTIPLE AND REPEATED NONPURULENT MICRO-EMBOLISM IN INFECTIOUS ENDOCARDITIS. H. U. GLUOOR and MAURICE GILBERT, Schweiz. med. Wchnschr. **56**:17, 1926.

In streptococcus endocarditis innumerable microscopic emboli may lodge in different organs without causing serious disturbances. In the skin they may give rise to purpuric spots of diagnostic value. Such emboli need not lead to metastatic abscesses, but may be followed by minute foci of necrosis which may result in minute scars.

Immunology

THE RELATION OF ANAPHYLAXIS TO IMMUNITY STUDIED BY PASSIVE SENSITIZATION IN DOGS. W. H. MANWARING, RALPH W. WRIGHT and P. W. SHUMAKER, J. A. M. A. **86**:1271, 1926.

If a normal dog is exsanguinated as completely as possible, and its blood volume restored by transfusion from an anaphylactic donor, the dog that receives the blood becomes typically hypersensitive. Twenty-four hours later, on intravenous injection with 1 cc. of horse serum per kilogram of body weight, there is a typical fall in arterial blood pressure, typical contractions of smooth muscle structures, typical cyanotic engorgement of the abdominal viscera and a complete loss of blood coagulability. Recovery is usually complete in from thirty to sixty minutes.

If in a similar way from 5 to 80 per cent of the total blood volume of a dog is replaced by transfusion from an immune donor, no suggestion of specific hypersusceptibility is conferred on the animal receiving the transfusion. On a routine test, twenty-four hours later, there is no fall in arterial blood pressure, no engorgement of the abdominal viscera and no reduction in blood coagulability.

This differs markedly from published results with rabbits and guinea-pigs, in both of which a passive transfer of from 10 to 25 per cent of the total serum volume from an immune donor renders the normal animal typically hypersensitive, in many cases sufficiently so to give fatal anaphylaxis.

In dogs, therefore, the difference between the sensitizing antibody and the immune antibody is not merely a quantitative one. The two antibodies apparently have wholly different physiologic properties.

ERYSIPELAS: V. OBSERVATION ON THE ETIOLOGY AND TREATMENT WITH ERYSIPELAS ANTISTREPTOCOCCIC SERUM. KONRAD E. BIRKHAUG, J. A. M. A. **86**:1411, 1926.

Further experimental evidence is advanced to prove that the etiologic agent in erysipelas is a specific type of *Streptococcus hemolyticus* and that the serum produced with this specific type of micro-organism possesses marked curative properties when administered early in the disease.

THE RECOGNITION OF A BIOLOGIC DIFFERENTIATION IN THE WHITE BLOOD CELLS WITH ESPECIAL REFERENCE TO BLOOD TRANSFUSION. CHARLES A. DOAN, J. A. M. A. **86**:1594, 1926.

There seems to be a definite incompatibility between the blood plasma of certain persons and the white blood cells of others, as shown by simple in vitro tests.

A definite biologic classification of persons according to white cell compatibility is difficult because at least twenty-seven different combinations are possible, many of them not infrequent. Approximately 40 per cent of the group of forty persons examined may be considered universal donors (group A);

5 per cent seem to have cells susceptible to all, or nearly all, plasma (group Z); nine different combinations are represented in the remaining 55 per cent, to which no arbitrary group designation has been assigned at this time.

AUTHOR'S SUMMARY.

THE RÔLE OF THE RETICULO-ENDOTHELIAL SYSTEM IN IMMUNITY. II. The COMPLEMENT TITER AFTER BLOCKADE AND THE PHYSIOLOGICAL REGENERATION OF THE RETICULO-ENDOTHELIAL SYSTEM AS MEASURED BY REDUCTION TESTS. C. W. JUNGEBLUT and J. A. BERLOT, J. Exper. Med. **46**:797, 1926.

Intravenous injections of India ink into guinea-pigs caused a decided drop in the complement titer which set in as early as fifteen minutes after the injection but did not reach its maximum for three hours. This drop was followed by a return to normal within the first twenty-four hours following the injection.

India ink mixed in vitro with guinea-pig serum adsorbs the complement almost immediately to its full extent.

By means of reduction tests (methylene blue and nitro-anthraquinone), it was shown that the respiration of the cells of the liver and spleen of guinea-pigs was markedly impaired for the first eight hours following an intravenous injection of ink. Evidences of a return to normal functional vitality, however, became apparent by the end of the first day after the injection.

AUTHORS' SUMMARY.

A DIRECT METHOD OF DEMONSTRATING THE ABSORPTION OF INCOMPLETELY DIGESTED PROTEINS IN NORMAL HUMAN BEINGS. MATTHEW WALZER, J. Immunol. **11**:249, 1926.

The serum of a hypersensitive patient on intradermal injection into a normal person sensitizes the site of injection to the substances to which the patient from whom the serum is obtained is sensitive. This is reported to be a simple, rapid and specific method for demonstrating the absorption of protein from the digestive tract. Such absorption appears to be more frequent than is supposed.

S. A. LEVINSON.

THE ANTIGENIC PROPERTIES OF EXTRACTS OF HORSE DANDER. II. THE ISOLATION OF TWO ANTIGENIC PROTEINS FROM EXTRACTS OF HORSE DANDER. W. T. LONGCOPE, D. P. O'BRIEN and W. A. PERLZWIG, J. Immunol. **11**:253, 1926.

As solutions of horse dander extract, when freed of protein by dialysis or chemical manipulation are inactive, and as lipoidal extracts of horse dander are inactive, it may be concluded that the antigenic substance or substances of horse dander extract are protein in nature.

Solutions of horse dander extract withstand heat for an hour at 100 C. at a neutral reaction of p_H 7.4 and at an alkaline reaction of p_H 9 without material impairment of their antigenic properties.

Horse dander extracts heated under the same conditions at p_H 4.5 form precipitates, and the supernatant fluid loses a considerable part of its antigenic property.

By iso-electric precipitation, two proteins were obtained from horse dander extract. The iso-electric point of one protein, present in large amounts, lay between p_H 3.2 and 3.8. The other protein, present in small quantities, remained in solution at varying degrees of acidity and alkalinity ranging from p_H 3.2 to 12.

Each of these proteins is capable of producing anaphylactic reactions in sensitized guinea-pigs and of causing skin reactions in patients allergic to horse dander.

These two proteins are biologically specific and can be differentiated sharply by their anaphylactic reactions.

S. A. Levinson.

The Antigenic Properties of Extracts of Horse Dander. III. Skin Reactions and Passive Transfer of Horse Dander Sensitiveness to the Antigens of Horse Dander Extract. D. P. O'Brien, J. Immunol. **11**:271, 1926.

The skin of the horse asthmatic (Reineke) which was highly sensitive to whole extracts of horse dander, was likewise sensitive to the two protein fractions of the extract differentiated by iso-electric precipitation.

The skin of a normal person was found to be readily sensitized passively with the injection of serum from cases of hay-fever, rabbit asthma and horse asthma, so that the passively sensitized areas reacted twenty-four hours later to injections of extracts of ragweed and timothy, extracts of rabbit hair, and extracts of horse dander.

The passive sensitization of areas of skin of a normal person by injection of serum from a horse asthmatic rendered these areas specifically sensitive to the two protein fractions of horse dander extract. Author's Summary.

Studies in Specific Hypersensitiveness. XIX. The Relation of the Inheritance of Atopic Hypersensitiveness and the Isoagglutination Elements (Blood Groups). Philip Levine, J. Immunol. **11**:283, 1926.

No evidence was obtained that hypersensitiveness is associated in inheritance with the blood group, as hypersensitive children may or may not belong to the same blood group as the sensitive parent.

Investigation on "Cold" or Autohemoagglutination. Li Chen-Pien, J Immunol. **11**:297, 1926.

Auto-agglutination in the case of a patient with syphilitic cirrhosis was studied. Agglutination took place only at room temperature, and the corpuscles separated again at 37 C. The serum agglutinated at room temperature corpuscles of all human blood groups.

A Study of Blood Groups Among the American Indians. Clara Nigg, J. Immunol. **11**:319, 1926.

The percentage occurrence of the four Landsteiner blood groups in two series of full-blooded Indians is as follows: First series, comprising 316 Indians of many tribes: group I, 70.89 per cent; group II, 27.21 per cent; group III, 1.58 per cent; group IV, 0.32 per cent; second series, comprising 457 Indians of the Navajo tribe only: group I, 72.65 per cent; group II, 26.91 per cent; group III, 0.22 per cent; group IV, 0.22 per cent.

Because of the unusually high percentage of group I, both the corpuscular and serum iso-agglutination elements were studied and were found to conform to those of specimens of true group I bloods. Author's Summary.

The Intracellular Proteins of Bacteria. I. Globulins. Casper I. Nelson, J. Infect. Dis. **38**:371, 1926.

The globulins obtained by autolysis and electrodialysis of the colon-typhoid bacteria grown on a synthetic medium appear to be specific precipitinogens, and it is suggested that precipitin tests of globulins may prove a means of studying group relationships between bacteria.

ARE THERE IMMUNOLOGIC STRAINS OF SPIROCHAETA PALLIDA? JOHN A. KOLMER, DOROTHY WILKES-WEISS and CAROLA E. RICHTER, J. Infect. Dis. **38**:378, 1926.

No evidence of immunologically distinct types of *Spirochaeta pallida* was obtained. Localization of *Spirochaeta pallida* and the subsequent course of the infection are influenced largely by the virulence of the organism, the method of inoculation and the susceptibility of the host. It is suggested that similar factors may explain differences in human syphilis.

THE NON-SPECIFIC ANTIGENIC EFFECT OF SPERMATOZOA UPON FERTILITY. S. J. FOGELSON, Surg., Gynec. & Obst. **42**:374, 1926.

In the rat conception can be prevented by the injection of spermatozoa of any species. This effect cannot be explained satisfactorily at present. The results do not cast any light on so-called idiopathic human sterility, but they may constitute a basis for further efforts to discover contraceptive methods. No indications were found from the study of seventeen normal married but sterile women that antibodies against human spermatozoa played any rôle in the sterility.

SEROLOGIC ANALYSIS OF LEPERS' SERUMS. O. SCHÖBL and J. RAMIREZ, Philippine J. Sc. **29**:305, 1926.

The blood of ninety-two lepers was studied; the amount of natural hemolysins and complement seemed to be about the same as in the blood of normal persons.

STANDARDIZATION OF TUBERCULIN AND PRECIPITIN TEST. C. C. OKELL and OTHERS, Lancet **1**:433, 1926.

This is a report on the result of a joint investigation as to whether tuberculins found to be equal (within the error of the test) to standard by the official Frankfort test on guinea-pigs could vary widely in their content of the active principles of "tuberculin," the substance used for the detection of tuberculosis in man and animals. Their observations may be summarized: The precipitation test does not necessarily measure the active principles of tuberculin on which its use depends. Satisfactory agreement in precipitin unit value was obtained by two different groups of workers by the precipitin test. This test apparently measures with a considerable degree of accurary a substance probably other than the active principle of tuberculin, and presumably the interesting precipitable substance of Mueller and Laidlaw. The "tuberculin" value of tuberculins which have been standardized by the official Frankfort method cannot in all cases be deduced from the precipitin test. The results obtained by subcutaneous, intracutaneous, and Pirquet tests on guinea-pigs and by the tests on tuberculous human beings and cows were in agreement. By these three methods a tuberculin of standard strength and two others of values approximately 10 and 5 per cent of standard were placed correctly in order of merit.

ON THE "AVIDITY" OF DIPHERIA ANTITOXIN. T. MADSEN and S. SCHMIDT, Ann. de l'Inst. Pasteur **40**:300, 1926.

By "avidity" of diphtheria antitoxin is meant the speed of its combining reaction with toxin. This is demonstrable in vivo as well as by the flocculation method of Ramon. Serums vary greatly in avidity while having a correspond-

ingly smaller range in antitoxin units. A serum with great avidity has much higher curative value than one of low avidity. Avidity remains almost constant in a given animal during immunization.

G. B. Rhodes.

The Relation Between the Neutralizing Power in Vitro of Antitetanic Serum and Its Immunizing and Curative Action. G. Tizzoni and P. Bardelli, Ann. d'ig. **36**:165 (March) 1926.

After performing numerous experiments with antitetanic serum, the authors reach the following conclusions: The antitoxic power of antitetanic serum varies considerably with different horses immunized with the same culture, as well as in serums of different origins. There is no correspondence between the antitoxic power and the immunizing power of the serums. There are differences which do not follow any rule. The antitoxic power remains unchanged when the serums are kept sterile without addition of preservatives. Antitetanic serums, even of different origins, show slight differences in immunizing value, contrary to the antitoxic power. The preventive dose of our serum, the dose at the onset of illness, and the dose twenty-four hours later stand in the relation of 1:4:140. The curative dose of our serum is smaller than that of other serums. Injections at the site of infection are more effective than injections at a distance or intraperitoneally. The relation between local and intraperitoneal injection is 1:1½.

B. R. Lovett.

Serotherapy and Congenital Allergy. Piero Brusa, Boll. d. Ist. sieroterap. Milan **5**:69, 1926.

Serum sickness of the accelerated type seen in persons sensitized by a previous injection of serum occurs in some children never before treated, and may often be anticipated by finding that the mother has received injections of serum. The regular course of desensitization is then advised if the child requires serotherapy. This allergic state is not strictly hereditary, for it is derived only from the mother. It cannot be passed on to guinea-pigs and is regarded as a cellular hypersensitivity. If the mother's history is negative, a prudent decision as to the urgency of intravenous or intraspinal serum injection should be made.

Ethel B. Perry.

Experiences in Antityphoid-Paratyphoid Cutaneous Vaccination. Enrico Benassi, Boll. d. Ist. sieroterap. Milan **5**:87, 1926.

Subcutaneous injections of typhoid and paratyphoid vaccines into rabbits and guinea-pigs were superior both to applications by friction to either unbroken or scarified skin, and to intradermal injections, for the production of immunity and of agglutinins and complement-fixation bodies. Opsonins appeared only after intradermal injections. The conclusions were that properly speaking there is no antityphoid-paratyphoid cutaneous immunity nor cutaneous vaccination, and that the antibodies produced were the result of resorption of the vaccine into the circulation.

Ethel B. Perry.

The Nature of the Blanching-Phenomenon. S. I. Zlatogoroff and W. S. Derkatsch, Klin. Wchnschr. **5**:445, 1926.

The capacity of a serum to blanch scarlatina exanthem is related to its content of specific antistreptotoxins (Schulz-Charlton substances). Active serums may be prepared by immunization against streptotoxin, against living,

virulent cultures of toxic streptococci, or against virulent scarlatinal material containing hemolytic streptococci. They cannot be prepared by immunization against inactive toxin or against dead streptococci which have been washed free from toxin. Serums active in producing the blanching phenomenon are also agglutinative for the scarlatina streptococcus and give complement-fixation reactions with antigens prepared from the desquamated skin of scarlatina patients.

ARTHUR LOCKE.

AIRPLANE OBSERVATIONS ON THE POLLEN CONTENT OF THE AIR IN SPRINGTIME. R. WIGAND, Klin. Wchnschr. **5**:508, 1926.

There is a relatively large concentration of *Pinus* and *Betula* pollens in the upper air in the springtime.

ARTHUR LOCKE.

INJURIES TO THE CENTRAL NERVOUS SYSTEM FROM VACCINATION. FRANZ LUCKSCH, Deutsche Ztschr. f. ges. gerichtl. Med. **7**:203, 1926.

Following vaccination there may arise disturbances in the central nervous system in the form of serous meningitis, of encephalitis with tetanus-like symptoms or with somnolence or paralysis of the eye muscles, and as lesions of the cord with the picture of anterior poliomyelitis. The mortality in the encephalitis cases may be high. The microscopic appearances in the encephalitis forms differ from those of epidemic encephalitis, particularly by the extensive participation of glia in the infiltrations and also because the white substances are involved in the inflammatory changes. The interval between vaccination and the development of the changes in the central nervous system is about ten days. The conditions about the point of vaccination appear to bear no relation to eventual nervous disturbances.

BIOLOGIC DIFFERENTIATION OF SERUM PROTEINS OF RATS AND MICE. R. OTTO and E. CRONHEIM, Ztschr. f. Hyg. u. Infektionskrankh. **105**:181, 1925.

A certain degree of differentiation between the serums of rats and mice was indicated in anaphylactic tests in guinea-pigs sensitized actively with rat and mice serums, or passively with immune rabbit serum. Precipitin and complement-fixation tests with the same rabbit serums did not give parallel results, and failed to differentiate the serums when the passive anaphylactic tests did.

E. B. PERRY.

THE INFLUENCE OF CHEMICAL LIGHT BATHS ON THE BACTERICIDAL PROCESSES IN THE BLOOD AND THE SERUM. V. GENNER, Acta radiol. **5**:172, 1926.

The author could not confirm the observations of Colebrook, Adinow and Hill that chemical light baths increase the bactericidal power of the blood.

THE DIAGNOSTIC VALUE OF THE MEINICKE REACTION. S. SHIMOMURA, Acta dermat. **7**:2, 1926.

The Meinicke and Wassermann reactions agreed in 89.1 per cent of cases in one series and in 91.5 per cent in another series. The results of the Meinicke reaction are satisfactory. It appears sooner in syphilis and lasts longer than the Wassermann reaction.

B. R. LOVETT.

THE CORRESPONDENCE BETWEEN THE INCREASED PHAGOCYTIC POWER OF THE LEUKOCYTES AND THE INCREASED BLOOD SUGAR AFTER INJECTION OF HYPERTONIC GLUCOSE SOLUTION. H. SHIMADA, Acta dermat. **7**:65, 1926.

No parallelism was found between the changes in blood sugar and the leukocytic phagocytosis following injection of hypertonic sugar solution. The maximum phagocytic power occurred after the hyperglycemia was nearly over. The latter continued for several hours after the injection. The sugar solution may act as a stimulant to the function of the leukocytes or to the immunizing mechanism of the organism, but the hyperglycemia itself apparently has no such effect.

B. R. LOVETT.

STUDIES ON THE MENINGOCOCCI. PART 4. ON THE AGGLUTINATION OF HEATED MENINGOCOCCI. SHOJI KONDO, Tohoku J. Exper. Med. **7**, 1926.

By the careful isolation of colonies immunologically, constant strains were obtained, many of which, however, were but slightly agglutinable. Heating the organisms to 100 C. for one-half hour increased their agglutinability; the nonagglutinable became agglutinable, the lightly agglutinating ones were moderately influenced, different colony descendants from a common strain reacted alike after being heated, and spontaneous agglutination was seldom induced. Such heated organisms reacted with antiserums from both heated and unheated organisms, while the unheated bacteria did not always agglutinate with either serum. From the antiserum for the heated cultures the unheated bacteria could absorb all the agglutinins, but from the antiserum for the unheated all the agglutinins for the unheated were not always absorbed by the heated cultures. The increased agglutinability thus tended to reduce the number of slightly differing strains.

ETHEL B. PERRY.

Tumors

CHORDOMA: A REVIEW, WITH REPORT OF A NEW SACROCOCCYGEAL CASE. MATTHEW J. STEWART and JOSEPH E. MORIN, J. Path. & Bact. **29**:41, 1926.

The authors report a case of chordoma in a man, aged 58, who had been discharged from the army in 1916 with a clean bill of health. He first noticed a lump in the sacral region in 1917, which continued to grow slowly until it became very large, in October, 1925, measuring 30 by 20 by 10 cm. The tumor was judged to be inoperable, but a large piece was removed for histologic examination. The picture was that of a notochordal tumor of low malignancy. A detailed histologic description is given, accompanied by excellent drawings in colors. Histologically, the tumor was divided into lobules of irregular size by strands of dense fibrous tissue which were continuous with the thick capsule. Many thin-walled vessels occurred in the fibrous trabeculae, some greatly dilated. Hemorrhages of various sizes occurred throughout the tumor, the larger ones accompanied by areas of necrosis. The general appearance of the parenchyma was that of highly vacuolated syncytium. Closer examination of the smaller lobules revealed individual polygonal cells which were clearly delimited. Vacuolation varied from practically none to huge "physaliphorous" cells composed of a nucleus with a narrow ring of cytoplasm surrounding a group of large vacuoles. Varying amounts of mucin were present; in places the mucinous degeneration was extensive.

The authors also give a summary of all the recent cases of chordoma. In 1922, Steward had collected a list of twenty-six cases which had been published up to that time. The total list now includes twenty-eight cases in relation to

the anterior extremity of the notochord and twenty-eight sacrococcygeal cases, with one in the lumbar region—fifty-seven cases in all. The authors discuss ecchordosis physaliphora spheno-occipitalis. These soft, gelatinous notochordal tumors found in the region of the dorsum sellae are without clinical significance, but are important as the possible starting point of chordoma. They report a case discovered at necropsy. In all, twenty-four cases of ecchordosis have been published.

Chordoma is discussed as to sites of occurrence, morbid anatomy, histology and its clinical aspects. The authors point out that the prognosis is bad in all cases of chordoma. The cases in which the tumor is located in the spheno-occipital region average about 2.8 years from beginning of symptoms to recurrence or death. Those in which the tumor is sacrococcygeal in origin average 6.4 years. Recurrences nearly always follow extirpation, but since the patient may have a respite of from three to five years in the sacrococcygeal cases, surgical removal should be attempted. A complete bibliography is appended.

E. M. Hall.

Technical

Sanocrysin and Experimental Tuberculosis. O. Bang, Ztschr. f. Tuberk. **44**:298, 1926.

Five bovine and three human strains of tubercle bacilli did not lose their capacity of growing in a dilution of 1:5,000 of sanocrysin. The bacilli that Møllgaard used in his animal experiments are of unusually low virulence. Bang repeated Møllgaard's chemotherapeutic procedures on calves and rabbits, using more virulent bacilli from fresh bovine lesions; he was not able to demonstrate any curative effect.

Max Pinner.

The Digestion of the Sputum with Antiformin (Uhlenhut) for the Demonstration of Tubercle Bacilli. W. Mueller, Ztschr. f. Tuberk. **44**:318, 1926.

In 1,000 examinations tubercle bacilli were found in 33.3 per cent by direct smear; after digestion with antiformin an additional 21.8 per cent of sputums were found to be positive.

Max Pinner.

Mátéfy's Seroreaction in Pulmonary Tuberculosis. H. Rosenhagen, Ztschr. f. Tuberk. **44**:321, 1926.

The results on 100 serums were unreliable. The reaction has apparently no significant diagnostic value.

Max Pinner.

Colorimetric Method for the Determination of Inorganic Sulphates in Urine, Blood and Milk. Shun-Ichi Yoshimatsu, Tohoku J. Exper. Med. **7**:119, 1926.

After the removal of the protein from urine, blood and milk, by the use of alum cream, the sulphates were precipitated with benzidine hydrochloride, dissolved in an iodine, potassium iodide and ammonia mixture, and calculations made from colorimeter readings. Figures from other authors are given for comparison. The inorganic sulphate of breast milk was found to be from 0.6 to 1.9 mg. per hundred cubic centimeters.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Oct. 11, 1926

FRANK SMITHIES, M.D., *President, pro tempore, in the Chair*

ADAMANTINE EPITHELIOMA. WARNER S. BUMP. (Henry Baird Favill Laboratory, St. Luke's Hospital, Chicago.)

This is a report of two adamantine epitheliomas and an account of Malassez' explanation of the origin of these tumors.

The enamel of the tooth is the product of a glandlike structure, the enamel organ, which is derived from an infolding of the buccal epithelium. The enamel organ proper is the result of intensive epithelial proliferation; only a few cells actually taking part in enamel secretion. After the crown is entirely formed, none of the epithelial structures has any function in man, and they remain only as isolated groups of characterless cells about the roots of teeth. In animals with numerous dentitions the epithelium remains active, forming enamel for the teeth of the various dentitions.

It is Malassez' idea that these atrophied cells may be stimulated to new growth by infection or trauma, forming tumors, the structure of which resembles the epithelial formations from which the proliferating débris is derived. He thus explains how these tumors may be solid or cystic with cells varying from squamous to cylindric or star-shaped ones.

The first tumor of the report was practically solid, occurring in the right side of the upper jaw of a man, aged 50, following the formation of an alveolar abscess present for eight years before treatment, and recurring three years after removal by the curet and electrocautery. It contained enameloblast-like cylindric cells and star cells, arranged much as in the enamel organ. The second tumor was infected, appearing in the left side of the lower jaw of a woman, aged 22, following the removal of an impacted third molar and present for two and one-half years before operation. It contained epithelial masses of squamous, cuboid and star-shaped cells.

From the reports of forty-eight observers it is found that fifty-three of sixty-nine tumors were in the lower jaw, fourteen in the upper jaw and two in both jaws. Thirty-two of fifty-five tumors were in women. The oldest patient was 75 years old, the youngest 8. The average age at which the tumors were first noticed was at 35.5 years. The average period of growth was 5.4 years.

Adamantine epitheliomas grow within alveolar borders, distending the bone, sometimes breaking through the bony shell into the maxillary sinus, orbit or even into the cranial cavity; but they do not spread by metastasis. However, if they are not completely removed at the first operation, they recur persistently.

(A complete report will be published in *Surgery, Gynecology and Obstetrics.*)

THE PURIFICATION OF DIPHTHERIA ANTITOXIN. EDNA RUTH MAIN. (Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago.)

This report includes the results of investigations which Dr. A. P. Locke and I have been making. Immune serums, such as diphtheria antitoxin, are extremely variable and impure preparations of the desired therapeutic sub-

stance. The potency of diphtheria antitoxin varies from 200 to 2,000 units per cubic centimeter. Its protein content varies from 6 to 12 per cent. The protective capacity per unit varies from a maximum value characteristic of fresh, highly avid serums, to a minimum value characteristic of aged and heated serums.

While it is necessary to protect a diphtheria patient against only a small amount of continuously introduced toxin, the unit effectiveness of the antitoxins now available is so low and the rate of absorption from the customary intramuscular injections so slow that relatively enormous doses must be administered to secure complete protection. For this reason, diphtheria antitoxin is almost universally subjected to concentration procedures since the injection of large fluid volumes or large amounts of foreign protein is not considered advisable.

Antitoxin is associated, mainly, with the pseudoglobulin fraction of the immune serum. This fraction constitutes less than 40 per cent of the total protein present, and various salt precipitation and electro-osmotic methods have been devised for the purpose of separating it from the other, undesirable proteins. These methods accomplish a concentration of about 500 per cent, and the concentrated preparations are in every way as effective as the raw serums and are much less active in causing serum sickness.

A greatly increased quantity of undesirable proteins can be precipitated from immune serums if these are first heated for some time at 60 C. Although a somewhat greater concentration is thus obtained, the unit effectiveness is so greatly reduced that the advisability of this procedure may be questioned.

Any separation of only from 60 to 80 per cent of associated serum proteins from a serum which contains less than 0.1 per cent of antitoxic protein does not greatly purify it. The residual preparation may still be less than 5 per cent pure.

A much higher degree of concentration has been obtained with immune serums of an anticellular nature, such as typhoid, meningococcus and pneumococcus agglutinins, and antisheep hemolysin. Rabbit antisheep hemolysin has been concentrated in our laboratory by a method of specific adsorption somewhat as follows: Fresh rabbit antisheep amboceptor serum is added to the antigenic red cells in such concentration that 90 per cent of the potency is absorbed. The hemolysin saturated cells are laked by the complement present and are centrifugalized and washed until comparatively free from adhering serum. The combining power of the cell stroma is then modified by extraction with ether, and the desorbed antibodies are recovered by suspension in a slightly acid solution. These solutions are of varying purity and avidity depending on the avidity of the original amboceptor serum. The best preparations contain 0.000,000,007 Gm. of nitrogen per hemolytic unit, and represent a concentration of 150,000 per cent.

These values, so far in advance of those obtained in the nonspecific fractionation of diphtheria antitoxin, seem to indicate that this antiserum might be purified more successfully by a method of specific adsorption on its antigen, diphtheria toxin.

Several difficulties attend this application. Diphtheria toxin, unlike erythrocytes or bacteria, is a soluble substance. It is so toxic that the immunization procedure is necessarily long drawn out. The serum produced is poorly avid and combines only slowly and loosely with toxin. It was not until 1920 that Nicolle observed that mixtures of diphtheria toxin and antitoxin precipitate

within a narrow range of concentration ratios. This observation was confirmed and extended by Ramon to include a method of titrating these substances in vitro.

Two cubic centimeters of a potent, fresh diphtheria toxin is measured into a series of micro test tubes. To these are added graded portions of the antitoxin. After standing for some time, floccules are observed in one of the tubes and, shortly after, in the contiguous ones. The first flocculating tube is found to contain a nearly neutral mixture of toxin and antitoxin.

Ramon analyzed the floccules and found them to contain three fourths of the total toxin and antitoxin of the original mixture, associated with less than 4 per cent of its nitrogenous constituents.

The floccules are not, however, a pure compound of toxin and antitoxin. They contain varying amounts of associated proteins, lipids and even inorganic salts. We have subjected them to ether extraction, electrodialysis and iso-

Comparison of Degree of Concentration of Diphtheria Antitoxin Obtainable by Different Methods

	Mg. of Nitrogen Associated With One Unit (Approximately)	Degree of Concentration: Mg. of Nitrogen per Unit Original Serum / Mg. of Nitrogen per Unit Final Preparation (Approximately)
Untreated plasma	0.007–0.07	1
Early salt precipitation methods, "insolubilization," nonspecific adsorption	0.016–0.02	2–3
Improved salt precipitation methods, electrodialysis	0.013	3–5
Iso-electric precipitation	0.003	12–15
Specific precipitation with diphtheria toxin: solutions of the precipitate		
1. According to Ramon	0.0025	15–20
2. With ether extraction	0.0020	18–25
3. With electrodialysis	0.0013	30–40
Extracts of the precipitate (iso-electric precipitation)	0.0005	60–100

electric fractionation, with the result shown in the table. Iso-electric fractionation has given the purest final preparation and is, at the same time, least injurious to the intrinsic avidity of the preparation. However, the largest single factor in influencing the purity of the final preparation is the avidity of the toxin for the antitoxin in the original flocculation mixture. Work is now in progress on the production of more avid raw materials, and we hope soon to obtain a purification of diphtheria antitoxin comparable to that already obtained with hemolysin.

The procedure of fractionation used is somewhat as follows: A mixture of toxin and antitoxin identical in composition to that in the first flocculating tube of the preliminary titration is allowed to stand until well formed floccules have separated and the supernatant liquid is brilliantly clear. After centrifugalization this supernatant is removed and the sediment washed five times with physiologic sodium chloride solution and twice with distilled water. A solution of this washed residue in dilute acid may then be heated, ether-extracted or electrodialyzed to destroy the combining power of the contained toxin. These procedures greatly increase the yield of recovered antitoxin but are injurious to the avidity. Iso-electric fractionation, on the contrary, gives small

yields of superior purity and avidity. The best preparation thus far obtained contains 0.000,003 Gm. of protein per antitoxic unit and represents a concentration of 10,000 per cent.

DISCUSSION

E. PRIBRAM: It is important theoretically as well as practically to know whether the purified antitoxin has the same curative effect as the original antitoxic serum. The proper concentration not only increases the amount of units and their ratio to the protein content, but also avoids serum sickness. I try to purify the serum, also to avoid the anaphylactic shock after a previous serum injection. In these respects, all attempts with different methods have been fruitless.

For the commercial use of the iso-electric method it would be necessary to know exactly the absolute loss of antitoxin units. The absolute loss of antitoxin units usually increases with the removal of proteins (purification). Losses were higher by using electro-osmosis than by using precipitation with salts. The high expense of serum concentration demands economic methods.

D. J. DAVIS: Can the method be used for the commercial production of antitoxin?

A. P. LOCKE: The comparative therapeutic usefulness of fresh and concentrated diphtheria antitoxin preparations is, indeed, an important question. Methods of antitoxin concentration which include prolonged heatings at 56 to 60 C. may decidedly reduce the effectiveness, per unit, of the original serum.

The purification of diphtheria antitoxin by selective adsorption on the toxin and consequent fractionation of the separated floccules does not, at this time, seem adapted to commercial, large-scale production.

E. F. HIRSCH: The purification of immune serum seeks to eliminate serum sickness. Purified hemolysins prepared from dog and rabbit serums, and the purified diphtheria antitoxins from horse serum have sensitized guinea-pigs specifically. The hope of eliminating serum sickness seems to lie in concentrating the therapeutic dose in a quantity of protein too small in a sensitive patient to cause symptoms.

PRIMARY SCLEROSIS OF THE PULMONARY ARTERY AND ITS BRANCHES. CHARLES M. BACON and CARL W. APFELBACH. (Presbyterian Hospital, Chicago.)

The clinical manifestations and the gross and microscopic alterations in the case closely simulated the clinical entity described by Posselt, and Eppinger and Wagner as primary sclerosis of the pulmonary artery. The interpretation of the case anatomically rested chiefly on determining an adequate cause for the marked hypertrophy of the wall of the right ventricle. None of the usual causes (mitral stenosis or other gross changes in the left cardiac cavities, hypertrophic emphysema, fibrous obliteration of the pleural cavities, fibroid tuberculosis of the lungs, bronchiectasis, etc.) was present. Microscopically, a universal and marked sclerosis of the pulmonary arterioles was found.

DISCUSSION

E. F. HIRSCH: Are the changes in the vessels limited to the intima?

CHESTER GUY: Are there like changes in other vessels of the body?

C. W. APFELBACH: The change in the vessels of the lungs is a fibrous tissue hyperplasia of the intima. The aorta is not altered.

LEUKOCYTES AND LACTATION. V. E. EMMEL.

This is a report of studies by V. E. Emmel, H. L. Weatherford and M. H. Streicher on the relation of leukocytes to lactation. Contrary to prevalent statements that no definite leukocyte reaction occurs in relation to the activities of the mammary gland, the results obtained demonstrate a pronounced leukopenia during active nursing in the albino rat. The results of a comparative study with reference to numerical neutrophilic and lymphocytic changes, lymphocytic azurophil granulation, erythrocytic reticulation, and polychromasia indicate fundamental differences between this leukopenia and that of inanition.

A quantitative study of leukocytic elements within the mammary tissues demonstrates an increased passage of lymphoid cells into the mammary alveoli and of neutrophils into the ducts in correlation with the circulatory leukopenia.

These correlated changes within the circulation and the mammary gland emphasize the rôle of leukocytes in colostrum and milk formation. Recent investigations demonstrating the fundamental importance of colostrum, on the one hand (Theobald Smith), and leukocytic secretions in growth (Carrel), on the other, together with evidence indicative of bactericidal properties in milk (Hanssen), lend increased significance to this participation of leukocytes in mammary activity.

(The complete article is published in the *American Journal of Anatomy.*)

DISCUSSION

D. J. DAVIS: Is there a constant leukocyte content of the milk of rats?

V. E. EMMEL: Apparently not.

CARCINOID OF THE APPENDIX VERMIFORMIS (BY TITLE). R. S. LEADINGHAM. (From the Department of Pathology, Emory University.)

Carcinoid of the appendix has, until recently, been considered rare. Because of the increasing practice of examining histologically tissues removed by operation, this tumor is being found more frequently.

It is relatively benign, occurs as a small, circumscribed, firm tumor within the lumen of the appendix or as an infiltrating growth along the entire length. It usually is confined to the mucosa and submucosa, seldom invades the muscularis and rarely penetrates the serosa. Its presence may be determined only by microscopic examination.

The nature of the tumor has occasioned considerable discussion. Some claim that the small, pale, spheroid cells characterizing most of the growths suggest endothelial rather than epithelial origin. However, the presence of columnar cells and the alveolar arrangement have led many to regard them as slow growing carcinomas.

The tumor here reported was removed incidentally during an operation for removal of an ovarian cyst, and was overlooked in the operating room and laboratory until microscopic sections were examined.

The tumor was 7 mm. long, and 3 mm. wide. It obliterated the lumen, and extended 3 mm. beyond the wall.

There were plaques of small, pale, spherical cells, and ill-defined acini, lined by cells of the columnar type. They were separated by a dense connective tissue stroma, in which focally were a few round cells.

The tumor was obtained from the surgical service of Dr. W. S. Goldsmith.

Fig. 1.—Carcinoma of appendix.

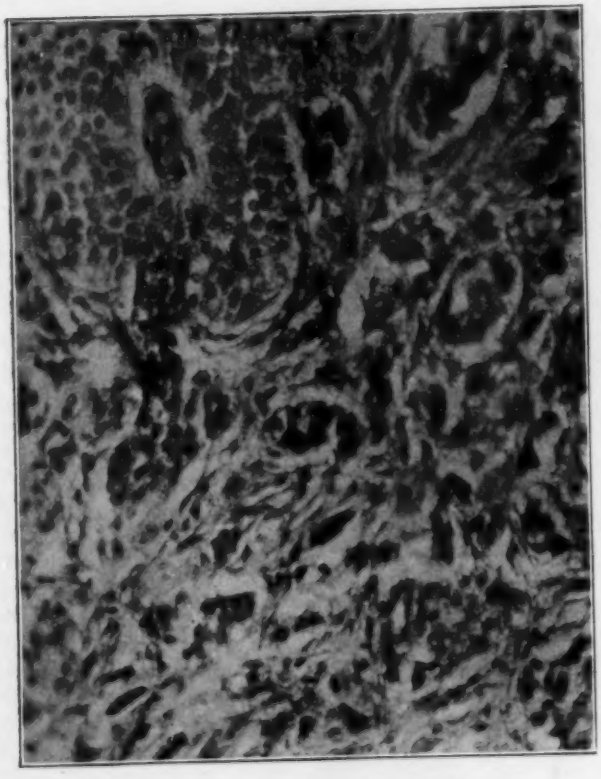


Fig. 2.—Carcinoma of appendix.

MINNESOTA PATHOLOGICAL SOCIETY

Oct. 19, 1926

GEORGE E. FAHR, M.D., *President*

ANEMIA IN CARCINOMA OF THE COLON. WALTER C. ALVAREZ.

Surgeons have noted frequently that the degree of anemia is greater in carcinoma of the cecum than in carcinoma of any other part of the intestine. The problem was to find some explanation of this observation; hence 1,200 cases of carcinoma of the colon in which operation was performed at the Mayo Clinic were analyzed. The degree of anemia could not be correlated to any factor except the surface area of the tumor. The symptoms resulting from stenosis are usually the first to call definite attention to the tumor; and since the cecum has the greatest circumference of any part of the intestine, stenosis develops later in the course of the disease here than elsewhere in the intestine. The larger surface of the tumor in carcinoma of the cecum results in more hemorrhage and more absorption of toxic bacterial products. A comparison with other tumors, such as carcinoma of the breast, shows that anemia is not dependent on the amount of tumor tissue present.

Dr. Alvarez also showed moving pictures of intestinal peristalsis.

E. T. BELL, Secretary.

Book Reviews

THE BACTERIOPHAGE AND ITS BEHAVIOR. By F. D'HERELLE, M.D., Directeur du Service bacteriologique du Conseil Sanitaire, Maritime et Quarantenaire d'Egypte. Translated by GEORGE H. SMITH, PH.D., Associate Professor of Bacteriology and Immunology, School of Medicine, Yale University. Pp. 629. Price, $8. Baltimore, Md.: Williams & Wilkins Company, 1926.

This third book in English dealing with the bacteriophage covers most of the important subject matter presented in the two former volumes, published respectively in 1922 and 1924, and much valuable material besides. The body of the text is divided into four sections: (1) the introduction, containing the historical setting and an important chapter on technic; (2) part I, dealing with the bacteriophage phenomenon including the effect of environmental conditions on the lytic agent and its reactions, the mechanism of action, its virulence, bacterial resistance and the species susceptible to the bacteriophagic influence; (3) part II, presenting the chief hypotheses relating to the nature of the bacteriophage, with an extended treatment of the author's conception of the lytic agent as a filtrable virus parasitizing bacteria; (4) part III, dealing with the bacteriophage as an antigen, its distribution in nature, its behavior in disease and in epidemics, together with its rôle in immunization practice and specific therapy.

The present work omits much interesting, though somewhat extraneous, material incorporated in the second volume, "Immunity in Natural Infectious Disease," which, notwithstanding considerable duplication ofthe subject matter, still possesses independent value. In the present text many workers will find of special interest and helpfulness the section dealing with technic, in which the author gives a clear exposition of his methods of filtration and other technical procedures of importance in a laboratory study of the bacteriophage. The section dealing with the effect of environmental conditions on the bacteriophage has brought this rapidly expanding aspect of the subject up to date through the incorporation of many recent examples. The subjects of bacteriophagic virulence and the nature and cause of bacteriol resistance and susceptibility have received considerable expansion, and a helpful section is added summarizing the present knowledge of the bacterial species found susceptible to lytic action.

In this volume the author finds it necessary to attempt to distinguish between true bacteriophagic lysis (bacteriophagy) and the false reaction (bacterioclysis), the latter representing a so-called "disease" of bacteria. The two phenomena are assumed to have no relation in point of cause. Twort's case of transmissible autolysis of staphylococcus, as also the transmissible autolysis of *Bacillus pyocyaneus*, is placed in the latter category. The nature and cause of bacterioclysis, however, is not discussed. The important and interesting opsonic action of bacteriophage suspensions receives valuable strengthening from fresh experimental data; likewise, the action of antibacteriophagic serums, about which the author's views have apparently undergone some revision. This phase of the subject is left in a somewhat uncertain state. Valuable additions have been made to the data on immunization practice with bacteriophage suspensions and their use in specific therapy, much new evidence having been incorporated from recent literature. Little that is new regarding the nature of the bacteriophage has been added. For d'Herelle, the arguments previously submitted suffice,

merely being repeated here. Undoubtedly with some satisfaction, however, he notes that Bordet seems to have abandoned his previous insistence on the purely hereditary aspects of the nutritive vitiation which he has assumed to be the cause of transmissible autolysis. The "splitter" or "chromosomal" theory of Bail hardly receives fair treatment. The "chemical" theories are disposed of effectively. However, the one theory of bacteriophage action which it seems probable will gain in importance in the near future (and which I hope to present in detail subsequently) is not mentioned by d'Herelle, although he believes that all possible theories have been considered.

In certain sections the book presents some startling misconceptions regarding the biology of the bacteria in relation to bacteriophage action. For example, the bacteriophage is set up as the agent to whose influence all the "mutations" of bacteria are due (a conception warmly supported by Bordet). If a high degree of variability is observed in the members of a bacterial culture, in morphologic, cultural, biochemical or serologic characters, the bacteriophage is at the bottom of it. If a culture manifests colony mutants, it is a sign that such a culture is "contaminated" with the bacteriophage. If a pure line culture manifests spontaneous agglutinative reactions or serologic reactions that are different from those of the parent strain, one must suspect that the bacteriophage has produced these results; only "ultrapure" cultures are constant in their characters. When a culture proves resistant to a race of the bacteriophage which at the same time attacks homologous, sensitive strains, it is because the former has come to possess an acquired resistance to the lytic agent, as a result of some previous contact with it. When serologic reactions in high titers occur with heterologous species (revealing what is now known to be the bacterial convergence of the R types), these are due to "mutations" created by the bacteriophage. When filtrable forms of bacteria occur, they are generated through bacteriophagic influence.

Of course none of these conceptions is really true; and one is naturally at a loss to understand how so much misinformation can have crept into otherwise so admirable a volume. But the difficulty is discovered when one observes that the great structure which d'Herelle has reared about the bacteriophage is grounded on the older biology of the bacteria — on the false monomorphic conception. A strict adherence to the postulates of monomorphism has made most easy, and at the same time most convincing, the elaboration of such a theory of bacteriophage action as d'Herelle has given us; but adherence to the dictates of this conception has more than once produced difficulties which d'Herelle has not been able to overcome — difficulties in the attempted solution of which he has been led into a field in which the lack of exact knowledge of his subject has caused him to present somewhat blindly both facts and theories. First and most important, d'Herelle takes no cognizance of the simple facts of microbic dissociation and their important bearing on the lytic phenomenon. He disregards the cyclogenic aspects of bacterial development and reproduction and treats each "ultrapure" culture as representing a homogeneity in population rather than as a heterogeneity of cell forms possessing highly variable potentialities for development and for autolysis, depending on the cyclogenic state. So far as d'Herelle's virus theory of the bacteriophage is concerned, I believe neither this nor any other theory that fails to take into consideration the cardinal phenomena of microbic dissociation, and the cyclogenic aspects of bacterial reproduction on which it must assuredly be based, can long survive. D'Herelle's great misfortune lies in the circumstance that he has attempted to understand and to depict the phenomena of pathologic variation in bacteria

before he has adequately surveyed the field of normal, dissociative variation. It seems safely predictable that this circumstance is the fact on which the entire virus theory of the bacteriophage will ultimately break down; and with it, it may be added, all purely "chemical" theories of transmissible autolysis.

Although the foregoing statements have been made in criticism of d'Herelle's theory of the nature of the bacteriophage, they fortunately may prove less disturbing to his more essential facts, although here also much supplementary information is demanded. One can but admire the splendid assembly of experimental data which the author has brought together in this book. When the data rest on his own experimental efforts, they cannot often be questioned. Whatever direction their explanation may take in the future, the value of these facts will undoubtedly remain; and with them, the important practical advantage to medicine which d'Herelle and others have amply demonstrated resides within the mechanism of this still unknown agent of bacterial destruction.

In conclusion, no small portion of the success which this volume is sure to attain will be attributable to the splendid translation by Smith. He has caught and made apparent to us the manifestly keen and enthusiastic scientific spirit lying behind d'Herelle's strikingly clear presentation of a complex and difficult subject.

A Manual of the Parasitic Protozoa of Man. By Charles F. Craig, M.D., Lieutenant-Colonel, Medical Corps, U. S. Army. Cloth. Price, $7. Pp. 569. Philadelphia: J. B. Lippincott Company, 1926.

The present work is an attempt to describe the entozoic protozoa of man in regard to their "morphology, life-history, relation to disease, prophylaxis, and diagnosis." Although the author has made good use of some of the related parasites of lower animals and free-living coprozoic protozoa, the work throughout adheres strictly to the medical point of view. By deliberate intention no discussion has been attempted of many of the broader zoological questions.

The general scope of the work is indicated by the chapter headings. Following a brief outline of the classification, structure, physiology and reproduction of the protozoa in chapter 1, there are four chapters devoted to the amebas, six chapters to the flagellates, six to the sporozoa and one to the ciliates. Malaria is given an extensive treatment covering four chapters. A useful technical appendix follows the chapters devoted to the different species. It is to be noted that the author omits the spirochetes, rickettsia and chlamydozoa. Most authorities will agree with him that the inclusion of these forms in the protozoa is at least questionable. At present, when there is considerable discussion as to what are the valid species of protozoa described from man, the author is to be commended on the fact that after he describes those species which he considers valid, he appends a description of doubtful forms. In the case of the intestinal amebas and flagellates there is a helpful discussion of coprozoic protozoa, which are not true parasitic species, but which grow readily in human feces and can often be cultivated from uncontaminated stools.

There are many points of more or less controversial interest about which it is interesting to note the author's opinion. He accepts the six well-known and established species of amebas living in man, but he considers that further work is necessary before Kofoid and Swezy's *Councilmania lafleuri* and *Karyamoeba falcata* and Faust's *Caudamoeba sinensis* can be accepted. Chatterjee's *Entamoeba paradysenteria* and Tibaldi's *E. macrohyalina* he believes probably are not valid species, but in the case of Smith and Weidman's *E. mortinatalium* he

considers further work necessary before the species can be dismissed. In regard to the pathogenicity of the intestinal flagellates, the author believes that under certain conditions *Giardia intestinalis* may be of some pathogenic significance not as a primary cause of diarrhea but as an added aggravation to other inflammatory reactions already present. He feels that the evidence is insufficient to prove that *Trichomonas hominis* or *Chilomastix mesnili* are pathogenic parasites, although he feels that they may play somewhat the same rôle as that suggested for *G. intestinalis*. Contrary to some protozoologists, he considers *Craigia hominis*, which was first described by him a well established species and considers that the available evidence indicates that it is pathogenic, causing a form of chronic diarrhea or dysentery. The author believes that the atypical parasites found independently by him, Emin and Stephens in patients suffering from tertian fever deserve the rank of a separate variety and uses the name *Plasmodium vivax minutum*. Similarly, he holds as established two parasites of estivo-autumnal malaria, *P. falciparum* and *P. falciparum quotidianum*. In his chapter on the ciliates, besides the well-known *Balantidium coli* he accepts Schandinn's *B. minutum* and *Nyctotherus faba*. Many protozoologists feel that the evidence for the existence of these two species is inadequate.

There is a helpful chapter on the prophylaxis and diagnosis of malaria. In his consideration of malaria control by mosquito reduction it seems to the reviewer that more attention should have been devoted to "species control," i. e., the concentration of attack on the one or two real anopheline offenders rather than on all anophelines, which has been so successful in the tropics. Furthermore, recent work would suggest that Paris green should have been considered as an efficient larvacide against the anophelines. If some of the recent work indicating that quinine has no effect on the sporozoite or infective stage of malaria is confirmed, it seems probable that some of the author's views on quinine prophylaxis will need revision.

To medical workers in general the book is to be commended as a clear, concise and accurate description of the protozoa of man. The book, itself, is well prepared, and the illustrations, many of which are new to such texts, are in general excellent.

MEDICAL REPORT OF THE HAMILTON RICE SEVENTH EXPEDITION TO THE AMAZON, IN CONJUNCTION WITH THE DEPARTMENT OF TROPICAL MEDICINE OF HARVARD UNIVERSITY, 1924-1925. By RICHARD P. STRONG, PH.B., M.D., S.D., Professor of Tropical Medicine; GEORGE C. SHATTUCK, A.B., M.D., A.M., Assistant Professor of Tropical Medicine; JOSEPH C. BEQUAERT, PH.D., Assistant Professor of Entomology, and RALPH E. WHEELER, A.B., Senior, Harvard University Medical School. Cloth. Pp. 313. Cambridge, Mass.: Harvard University Press, 1926.

This expedition to the Amazon was made chiefly for geographic exploration and medical investigation. The results of the latter are dealt with in the present report, although sufficient geographic facts are included to orient the reader. The work of the expedition was carried out in that portion of equatorial South America extending along the Amazon from its mouth on the east to the River Branco on the west.

Part I of the report by Drs. Strong and Shattuck and Mr. Wheeler deals with the more strictly clinical aspects as well as the etiology of various pathologic conditions in man and other mammals. Following a general description of the Amazon forest and its inhabitants there are chapters on the spirochetal infections, chronic inflammatory and ulcerative processes of the skin, leish-

maniasis, leprosy, malaria, splenomegaly, trypanosomiasis, blastomycosis, various parasitic infections of animals and pathologic conditions produced by certain of the insects and arachnids. Part II by Dr. Bequaert deals with the various Arthropoda of medical and economic importance that were collected during the expedition. In this section not only are a large number of arthropods listed, but various notes on the structure, habits, importance, pathologic effects and preventive measures of certain species are also appended. Part III is a collection of miscellaneous reports. The first is an interesting series of observations by Dr. Shattuck on subjects of medical, economic and geographic interest. Appended to this chapter is a list of birds, beasts, reptiles and fishes seen on the Branco, Uraricuera and Parima rivers. The second chapter is a description by Dr. J. H. Sandground of a new cestode, *Atriotaenia parva* from the "coati" *Nasua socialis*. The final chapters by Dr. Bequaert describe a dipterous parasite of a snail and list the land and fresh water molluscs obtained during the expedition.

The wealth of detail throughout the report makes it impossible to do the authors justice in a general review. The discussion under each subject is not limited to the original observations of the members of the expedition, but includes a general consideration of the broad aspects of the problem and a digest of the literature. Furthermore, certain important diseases, for example, yellow fever and Chagas' disease, are discussed in detail even though they were not actually encountered during the expedition. The report will be a necessary addition to the shelves of all workers interested in any of the subjects discussed. In fact, the only criticism is that one wishes that the members of the expedition could have covered an even greater range of subjects. Finally, the book itself is an excellent example of the bookmaker's art.

SURFACE EQUILIBRIA OF BIOLOGICAL AND ORGANIC COLLOIDS. By P. LECOMTE DU NOÜY, D.Sc. With Introduction by ALEXIS CARREL and ROBERT A. MILLIKAN. Cloth. Price, $4.50. Pp. 212. New York: The Chemical Catalog Company, Incorporated, 1926.

This is a record of the explorations of a physicist in what Dr. Carrel terms "the jungle of physiological phenomena." It begins with a simple and accurate method of examining the surface tension of colloidal solutions.

The surface of a solution differs from its interior in that its constituent molecules are not attracted equally in every direction. The inward attraction is not ordinarily entirely balanced by an outward attraction and there is a resultant contractile strain or tension. The strain is lessened when substances become dissolved which have a lower affinity for water than water has for itself. Such substances displace water from the liquid surface and, if present in sufficient quantity, gradually form a solid surface film.

This gradual surface accumulation has been studied by Du Noüy in such interesting solutions as sodium oleate, egg albumin and normal, immune and heated serums. He has been able to calculate, by an experimental method reported with meticulous accuracy and regard for detail, the thickness of a surface film, the dimensions of its component molecules, and the value of the Avagadro constant. He has found differences in the physicochemical behavior of normal and immune serums that are enormously suggestive.

". . . It has been experimentally demonstrated in this book that the proteins and other substances which constitute living matter have a tendency to concentrate at interfaces. They even carry with them part of the salts which, if alone in a solution, would show the opposite tendency. The precipitation

or the coagulation of proteins may in certain cases be facilitated by this accumulation of the molecules. But a still more important conclusion can be drawn: i. e. that the most probable configuration of equilibrium of such a system is the cell form."

Du Noüy's experimental and deductive methods are ingenious and his conclusions important.

BIOLOGICAL RELATIONS OF OPTICALLY ISOMERIC SUBSTANCES. By ARTHUR R. CUSHNY, M.A., M.D., L.L.D., F.R.S., Professor of Pharmacology and Materia Medica in the University of Edinburgh (Formerly in the Universities of Michigan and London). Published for the Johns Hopkins University. Baltimore: The Williams & Wilkins Company, 1926.

The important relationship of biologic and pharmacologic activity to physical qualities and chemical constituents cannot be demonstrated by a better example than the biologic relations of optically isomeric substances discussed by the author. After a short and clear explanation of the rotation of polarized rays by polarizing crystals, he gives an interesting historical review of the discovery of optically isomeric substances by Pasteur (1845). He likewise reviews Le Bel's and Van t'Hoff's explanation of the presence of an asymetrical carbon atom in the molecule of isomeric substances. The author also presents much diligently collected material on the biologic character of many optically isomeric substances.

Some optically active bodies form compounds with the alpha or with the beta type of the racemic pair in such a way that these types differ in their physical properties and chemical reactions (solubility of the compounds and salt formation, for instance). In these compounds the isomers, which no longer form mirror images, can be separated. The selection of only one of the optically active types by enzymes may be made similarly. Optically isomeric substances differ further in their pharmacologic action, just as they differ in their reactions with various enzymes or with optically active substances of known structure such as alkaloids. The explanation for that will be that different tissues may select different isomers as do the enzymes, one of which destroys the levorotatory the other the dextrorotatory. This selection may cause an alteration of the physical qualities of the two types of the racemic bodies.

The author's work on the biologic relations of optically isomeric substances was suddenly ended by his death. It is hoped that Dr. Cushny's labor will be an impetus to other biologists to continue his investigations.

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